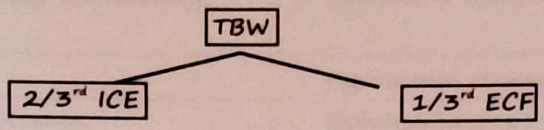
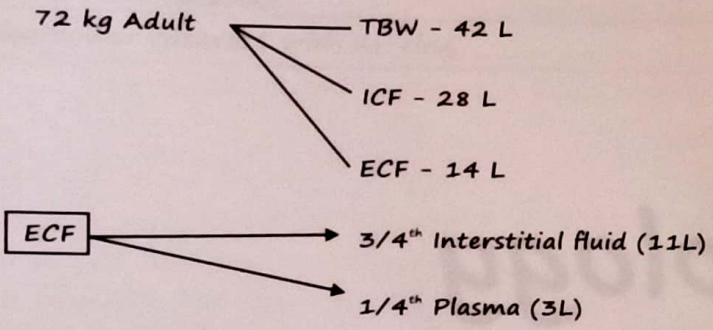
- Body Fluid compartments
- Concepts
- Cell Membrane
- Transport Processes
- Body Fluid Compartments

Total Body Water (TBW) = 60% of body weight = (0.6%) x Body wt



ICF - (0.4) x Body wt.

ECF - (0.2) x body wt.



→ Blood = 8% of body weight
→ Plasma = 5% of body wt

Measurement of Body Fluid Compartments

→ **Dye Dilution/ Indicator Method - based on Stuart Hamilton principle.**

I - Initial amount of dye injected

C - Concentration of dye after it got uniformly dispersed

$V = \frac{I}{C}$ (V = Volume of compartment)

A- Amount of dye that left the compartment and enter cells/ excreted

$V = \frac{I-A}{C}$

Various Indicators used for measurement: -

→ TBW - Deuterium oxide (D_2O)
- Tritium oxide ($3H_2O$)
- Antipyrine / Aminopyrine

Criteria for TBW - Dye should disperse in all compartments
- Almost non-existent membrane

→ ECF = Non-metabolizable saccharide

- INULIN (Best) – Stays in ECF
  – does not bind to plasma proteins
- Sucrose
- Mannitol

→ **ICF** = (TBW – ECF) indirectly measured
→ **Plasma** = Radio-Iodine (1^{131}) labeled albumin
→ **Red cell volume** → ^{51}Cr – tagging of red cells

Disturbances of Body Fluid Compartments

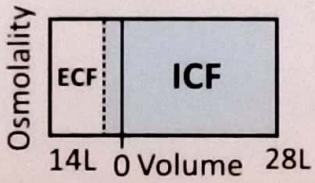
→ **Dehydration** (water lost form ECF)

– **Isotonic**

- Sodium and water lost from ECF in equal proportions
- No slight of water

Volume contraction
Patient is isotonic

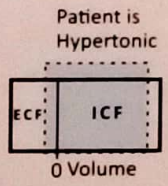
Osmolality : 300 MOsm/L
ECF Volume Shrunken



- Seen in – GI Fluid loss
  – Burns
  – Hemorrhage

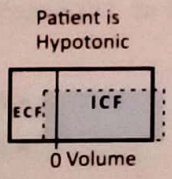
Hypertonic

- Only water is lost
- Seen in – Diabetes Mellitus
  – Diabetes insipidus
  – Alcoholism
  – Lithium salts



Hypotonic

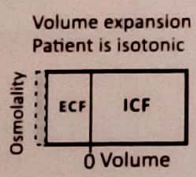
- Na+ loss >>> Water loss
- Seen in – 1 Hypoaldosteronism
- ECF water Shifts into ICF



Overhydration (volume gained in ECF)

– **Isotonic**

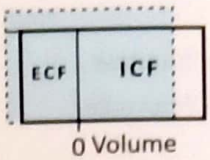
- Oral / IV Isotonic NaCl



Hypertonic

- Oral /IV Hypertonic NaCl

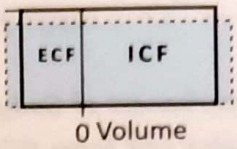
Patient is hypertonic



Hypotonic

- Only water gained to ECF
- Seen in SIADH (Syndrome of Inappropriate ADH secretion) and ↑ ECF vol → Atrial Filling pressure → ANP release → Kidney causing Natriuresis and Diuresis
- Ultimately: Euvolemic Hyponatremia

Patient is hypotonic



Note:

- If osmolarity of fluid consumed < 1200 mOsm/L – Overhydration
- If osmolarity of fluid consumed > 1200 mOsm/L – Hypertonic Dehydration

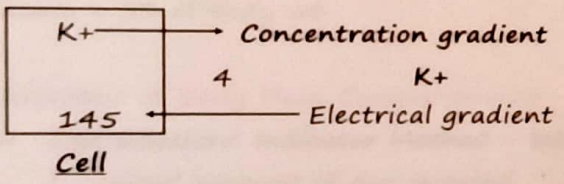
Reason: Max concentrating ability of kidney is – 1200mosm/L. In 1L of urine maximally 1200mosm/L can be excreted and If 1500 mOsm/L consumed – urine output have to be >1 L- Extra water being lost. Hence causing - Hypertonic Dehydration.

Concepts

→ **Milieu Interior** (coined by Claude Bernard)
Means internal environment of body → i.e internal Environment for the cell which is → E.C.F

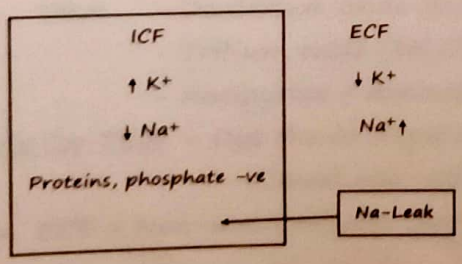
→ **Homeostasis** (Coined by Water F. Cannon)
Maintaining constancy/stability in the Milieu interior .

→ **Equilibrium**



- When concentration Gradient = Electrical gradient = No net movement of K^+ → Equilibrium.
  Steady state → eg. Blood glucose maintained at 100 mg%

Equilibrium	Steady state
• Two adjacent compartments • Two equal but opposite forces balanced out • No ATP's needed to attain equilibrium	• May involve one compartment also • Not necessary • ATPs needed



→ ICF:- ↑ K^+, ↓ Na^+; ECF:- ↓K^+, ↑ Na^+

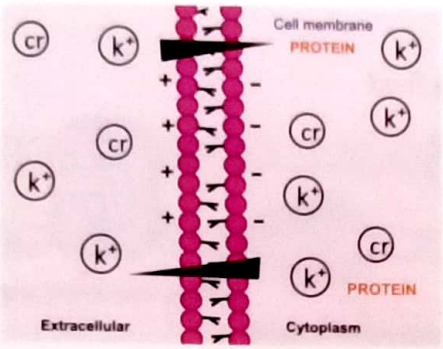
Exception:- Endolymph (ECF): - High conc^n of k^+

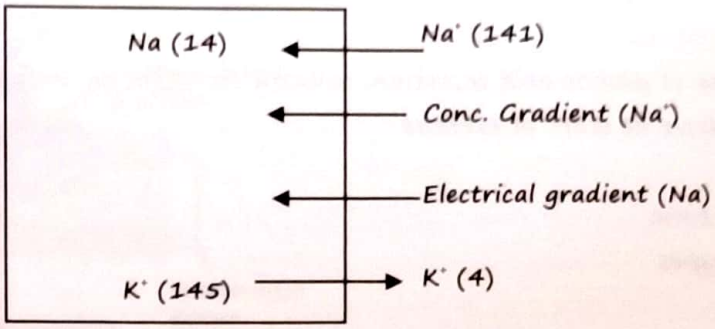
- Diffusible cations move through memb to attain equilibrium.

→ Excess anions in ICF due to impermeant anions –Phosphates and Proteins

- To achieve equilibrium equal number of cations to be pulled into a cell : - Na^+ leak.

→ This is known as – Donnan Equilibrium.





Na^+ - Concentration gradient
Electrical gradient
→ Outside to inside

K^+ - Conc. gradient (inside to outside)

- Electrical gradient (outside to inside)

• Concentration gradient – is for individual ion

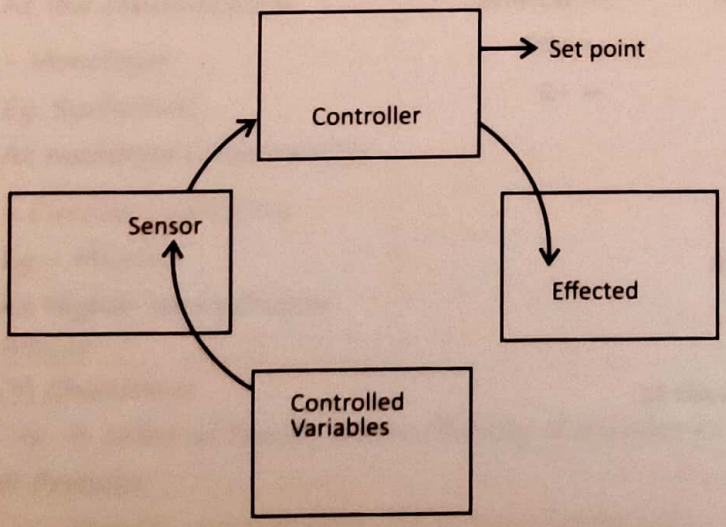
• Electrical gradient – created by all +ve and –ve charges

Homeostasis

→ **Regulatory Mechanisms**

- Feed Forward

- Feedback → Negative / Positive



- There are controlled variable (CV) in milieu interior
- Each variable has a sensor which senses disturbance / value of CV
- Value sent to controller
- Controller compares it with set point and takes action via effector organ

→ If Disturbance in CV → it feedbacks to controller = **Feedback mechanism**

→ If controller anticipates disturbance and takes necessary action = **Feed Forward Mechanism**

Feed-Forward- No lag time

Eg:-

→ Cephalic phase of gastric acid secretion, salivary secretion on seeing food

→ ↑ ventilator drive at start of exercise

Feedback - Lag time

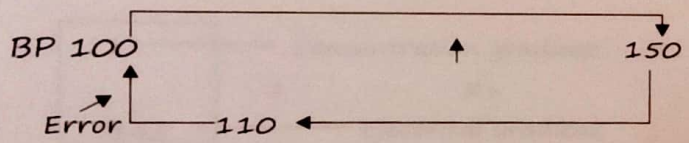
→ It is of Two types

- Negative
- Positive

Negative feedback

- Controller takes opposite action
- Error is minimized
- Efficiency is measured in terms of → GAIN OF Negative Feedback

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}} \quad ; \quad \text{Gain} \propto \text{efficiency}$$



$$\text{Gain} = \frac{40}{10} = +4$$

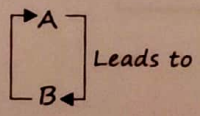
	Gain
• Kidney–body fluid mechanism in BP regulation	→ Infinite
• Temperature regulation	→ +33
• Baroreceptor mechanism	→ +2

Servo Mechanisms

- Have no fixed set point, hence no fixed Gain

  Eg. Muscle spindles in regulation of muscle length

Positive feedback

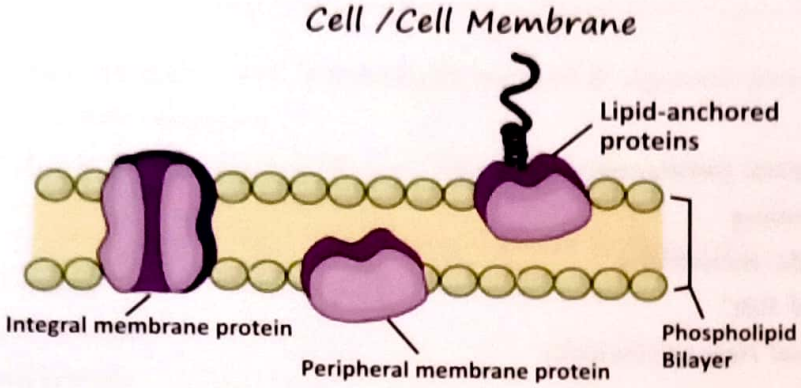


- Error is amplified
- Vicious cycle

Eg:- 2nd stage of circulatory shock (vicious cycle)

- Oxytocin in parturition

- Platelet plug or clot formation
- Action potential: - from RMP to threshold
- LH surge → Ovulation
- Head's paradoxical reflex (distension leads to more distension of lungs)
- Micturition reflex



→ Lipid bilayer with proteins embedded (Fluid mosaic model)
→ Most accepted mechanism – Singer Nicolson Model
→ 3 constituents (surface area)
- Carbohydrates (3%)
- Lipids (42%)
- Proteins (50% - 55% of SA. Of cell memb)

Note:- By dry weight – Lipids: Proteins – 1:1

Carbohydrates

→ 3% of total, and provides asymmetry to membrane
→ Many of carbohydrate are responsible for Immune Reactions

Lipids

(a) **Phospholipids (max concentration)**

→ When membrane is Injured - healing occurs by hydrophobic interactions Hence, our cells membrane is self sealing lipid bilayer.

At low concentration
- Monolayer
Eg. Surfactant
At moderate concentration
- Circular aggregates
Eg:– Micelles
At Higher concentration
Bilayer

(b) **Cholesterol**

→ Is called as fluidity buffer (fluidity of membrane is determined by it)

© **Proteins**

→ Protein concentration varies from cell to cell
- High proteins: - Inner Mitochondrial membrane (76%)

- Presynaptic membrane
- High lipid (low protein):- – Schwann cell membrane
- Oligodendrocyte membrane

→ Protein concentration varies from time to time
- depends on protein turnover rate

Types of membrane Proteins

→ **Integral** – spans the membrane eg. GPCR
- for ligand binding

→ **Peripheral** – attached on one side of membrane (inside/outside)
- involved in cell to cell signaling

Note:- GPI–linked proteins:- CD59, DAF in RBC membrane
→ They prevents complement mediated lysis of RBC
→ In case of Defect: PNH (Paroxysmal Nocturnal Hemoglobinuria)

Junctional Complexes

Desmosomes (Macula Adherens)
→ Membrane Proteins involved are
- Desmoplakin
- Desmoglein

→ Present with ↑ Tensile Strength – skin and in region with high wear and Tear – Gums, Cervix.

Gap Junctions

→ Low resistance passages between 2 cells
→ Seen in
- Heart
- Smooth muscle of gut
- Retina
- Inferior olive

→ Formed from protein connexon (6 subunits of connexins)

Defective Gap Junctions/ Connexin are present in:-

→ Adjacent schwann cells – Charcot Many tooth Disease (Connexin -32)
→ Idiopathic Atrial fibrillation – (connexin-40)

Tight Junctions (TJ) / Zonula occludens

→ Selectively permeable
→ Membrane proteins forming TJ are:- Claudins
- Occludins
- JAMs (Junctional Adhesion molecules)

Eg. - Blood Brian Barrier and Gut lining.

Filamentous Proteins in Cells

	Diameter	Examples
Microfilaments	7 nm	Actin (contractile process)
Intermediate filaments	7.25 nm	Keratin
Microtubules	>25 nm	Dynein, kinesin, cilia, flagella (11+2 arrangement)

→ Microfilaments and Microtubules involved in dynamic structure of the cell: intermediate filaments form stable structure

→ Drugs preventing microtubule assembly – Vincristine, Vinblastin, Taxels

Transport Proteins in Membrane

→ Pores

→ Channels

→ Carriers

→ ATP dependent Transporters

Pores

→ Always open. Eg- Aquaporins, perforins

Channels

→ Involved in simple diffusion of water soluble substances/ ions

- Leaky channels (Na^+ leaky channels in all cell membrane)
- Gated channels

Gated channels

→ **Voltage gated**
- Na^+ channels in nerve membrane.
- Nav 1.8 (Tetrodotoxin resistant present in primary afferents of pain)

→ **Ligand gated/Ionotropic Receptor Associated channels**
- Nicotinic Ach R (Ganglion cells/ NMJ)
- GABA- A

→ **Cyclic nucleotide gated channels (Metabotropic Receptor)**
- HCN (funny channel) in SA. Node
- $GABA_3$
- Muscarinic Ach R

→ **Time – gated channels**
- Slow Ca^{2+} channels in Heart
- Na^+, K^+ channels in nerve membrane

→ **Mechanically gated channels**
- Eg. Touch Receptor in skin

→ **Chemical gated channels**

- O_2 sensitive K^+ channel – LUNGS, Carotid body
- ATP – Sensitive K^+ channel – Systemic vascular smooth muscle, pancreatic -cell.
  - Hypoxia → Causes vasodilation elsewhere - systemic vascular smooth muscle (ATP sensitive K^+

channel) but in Lungs → it causes vasoconstriction (O_2 sensitive K^+ channel) (Pulmonary vascular smooth muscle cell)

- Lungs → Hypoxia → K^+ channel close → ↑K^+ in smooth muscle cell → depolarize → Contract
- Systemic vessels → Hypoxia → ↓ ATP → K^+ channel remain open → K^+ leaks out → vascular smooth muscle Hyperpolarize → Relax

Note:- Pancreas – SUR (Sulfonylurea Receptor on this ATP sensitive K^+ channel)

Study of channels

→ **Patch Clamp Method** (for single ion channel)

Note: - Voltage clamp for changing voltages

- Cathode Ray oscilloscope for Action potential

Poisons / Blocker of channels

Na^+- Tetrodotoxin, Saxitoxin

K^+- Tetraethyl ammonium, Mamba snake venom

Carriers:- They are Involved in:

→ Facilitated diffusion (uniport: Single substance at a time)

→ Secondary Active Transport – (carry two substances at a time)

- Symport (in same direction)
- Antiport (opposite direction)

→ Glucose enters all cells of body by facilitated diffusion via GLUTs except in – GIT and kidney.

→ Entry into cells – Secondary Active Transport (SGLT) and Exit – GLUT-2.

ATP- dependent Transporters

→ Pumps /ATPases– Na^+-K^+ ATPase, SERCA-J involved in Primary Active Transport

→ ABC transporters (ATP Binding cassettes)

- One part bind to ATP, other part and act as channel / carrier. Eg. MDR, CFTR, SUR.

Tips to remember transport proteins

7 → GPCR (7 transmembrane subunits)

6 → Connexon (6 subunits/ connexins)

5 → Ligand gated channels (pentameric)

4 → Voltage gated channels (Tetramer)

3 → G-protein (ENac has 3 subunits)

2 →Integrins (dimmers)

Transport Processes

→ **Across the membranes/ cytopempsis**

- Endocytosis
- Exocytosis

→ **Through the membranes**

- Osmosis
- Diffusion

- Active transport

→ **Across The Membrane**

- **Endocytosis**

- Substances that enter cells by endocytosis are:-
- Large molecules
- Particular matter
- Bacteria
- Foreign substances

Two types:-

→ **Phagocytosis** – Solids enter cells (cell eating)
Eg. Bacteria entering WBC

→ **Pinocytosis** – Liquids enter cells (cell drinking)
Eg. Soluble proteins enter the cells

Based on Mechanism:-

- Constitutive Endocytosis (continuous/ without any signal)
  Eg. Water soluble vitamin entry
- Clathrin mediated endocytosis (Receptor mediated)
  Eg. LDL enter steroidogenic cells
- Caveolin mediated/ Potocytosis
  Eg. Folate entry into cells

→ **Exocytosis (cell vomiting)**- Liquids released out of cell – Reverse pinocytosis.

- **Constitutive/Continuously**: - Ig secretion by plasma cells
  : - Mucous secretion by goblet cells
- **Regulated exocytosis** – Eg. Neurotransmitter secretion at synapse

→ **Through the membrane**

- **Osmosis**

- Movement of water from low solute concentration to high sodium concentration

Note: - Bulk Flow: - Water moves in bulk and drags Na^+ along with/solvent drag. Eg – Descending limb of loop of Henle
- CSF Reabsorption

Osmolarity – per litre of solution (Temperature Effects)

Osmolality – per kg of solvent (Not affected by temperature)

- Serum osmolality (mOsm/kg of H_2O) = $(2.1 \times Na^+) + (\frac{glucose}{18}) + (\frac{BUN}{28})$

- **Diffusion**

Passive transport (No ATP needed);Net movement → Downhill transport.

Two Types:-

- Simple (by virtue of kinetic energy)
- Facilitated diffusion (by carrier)

Simple Diffusion - Through lipid bilayer via channels

Factors affecting Rate of simple Diffusion

- → **Lipid solubility** - $Co_2 > O_2$, lipid soluble – faster diffusion
- → **Number of channels** - $K^+ > Na^+$, so K^+ diffusion is faster
- → **Temperature**
- → **Surface area**
- → **Thickness of membrane** (inversely related)
- → **Size /mol wt/ Radius (inversely related)**
  - Hydrated Na^+ is larger than Hydrated K^+ so hydrated K^+ diffuses faster
- → **Concentration gradient**
  - Larger the gradient, faster diffusion

	ECF	ICF
Na^+	141	14
K^+	4	145

  - K^+ - Wider gradient → diffuses faster

Note:- Membrane is 50-100 times more permeable to K^+ than Na^+. Hence, K^+ is most diffusible ion.

- → **Pressure gradient (for gases)**
  - Greater the gradient – Faster the diffusion

  Eg:- Hyperbaric O_2 given – alveolar pressure ↑ → gradient increases → faster diffusion
- → **Electrical gradient**

  Eg. Cation move from higher number of charges to lower charges

Facilitated Diffusion:- Characteristics

- → Saturability
- → Specificity
- → Inhibition

Eg. Glucose enters all cells of body except kidney and GIT by facilitated diffusion via GLUTs (carriers).

GLUT-3 – Brain

GLUT-4 – Adipose tissue, Muscle

GLUT-5 – Fructose Transport

Non-ionic diffusion (Diffusion trappinig)

- → Non-ionic forms more diffusible → diffuse to another side – acquire an ion now cannot diffuse back
- → Mostly seen with acids and basis

Eg – Aspirin entry into partial cells

- NH_3 buffering in Kidney ↑trapped as Nh_4^+

Active transport

- Uphill transport (Low → High concentration)
- ATP needed
  - : Directly : Primary Active transport
    - Eg. Na^+ - K^+ ATPases pumps, Serca
  - : Indirectly: Secondary Active Transport

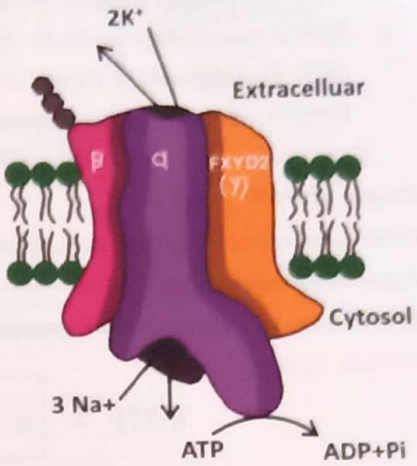
Symport /Co-transport

- Eg. Glucose entry into cells of GIT, Kidney via SGLT

Antiport / counter transport/ Exchange

- Eg:- Na^+ Ca^+ exchanger in heart (3 Na^+ : 1 Ca^{2+})
- Cl Hco_3 exchanger in RBC memb (Band 3/ AE - 1)

Na^+ - K^+ pump (discovered by Jens Skou)



3 subunits (some author - 2 subunits)- α ,β,γ

α - **Subunit catalytic-sites**

→ Na^+ binding site
→ Phosphorylation site } **Intracellular**
→ ATP binding site

→ K^+ binding site } **Extracellular**
→ Ouabain binding site

(Digitalis and K^+ competes for the 2 binding sites on external site)

β-subunit 3 glycosylation sites

Activity of pump: - Binds 3 Na^+ from inside - takes them outside
Binds 2 K^+ from outside - and taken in

Functions:-

→ Opposes Donnan Equilibrium
- Leaking Na^+ into cell is sent out by the pump, otherwise cell will swell and burst.

→ Regulates the cell volume.
→ Contributes in BMR (40% ATP spent on Na^+ - K^+ ATPase Pump : Neurons 70%
→ Recharging (after depolarization and repolarization)
→ Electrogenic → 4mv contributed to RMP (-86 mv by diffusion)

Stimulators and Inhibitors of pump

Stimulators	Inhibitors
→ Thyroid (↑ BMR by ↑ pump activity)	→ Digitalis
→ Aldosterone (↑ Number of pumps on basolateral side)	→ Dopamine (in kidney)
→ Catecholamines (in muscles)	→ Dinitrophenol
→ Insulin	

Nerve-Muscle

- RMP
- Action Potential
- Nerve
- Muscle

RMP - Resting membrane potential

→ All cells have membrane potential
- Red cell, epithelial cell = -8 to -20 mv
- Smooth muscle cells = -35 to -45 mv
- SA node = -55 to -65 mv

- Nerve = - 70 mv
- Skeletal Muscle, purkinje fibres = - 90 mv

→ ECF is considered to be 0- for all cells, except:- Hair cell in cochlea

ECF: Endolymph: - Excess K^+

RMP = +80mv (Endolymphatic potential) so Transmembrane electrical Gradient = 150 mv (Highest in body)

Origin of RMP (-90 mv)

When ion moves by conc. Gradient and reaches equilibrium, that of time cell gets charged inside

Equilibrium potential.

Equilibrium potential for an ion calculated by Nernst equation

Nernst Equation

$$EMF = \boxed{\pm 61 \times \log \frac{C1}{C2}}$$

C1 = Initial concentration

→ Equilibrium potential for Na^+ = +61 mv

→ Equilibrium potential for K^+ = - 96 mv

Note:- K^+ is the greatest contributor for RMP (membrane is 50-100 times more permeable to K^+)

→ Equilibrium potential for Cl^- = - 91 mv (closest to RMP)

→ If all 3 ions moving simultaneously and reaching equilibrium then charge on membrane given by - GHK equation.

Goldman's constant field/ Goldman's Hodgkin Katz Equation

→ Considers 2 Factors

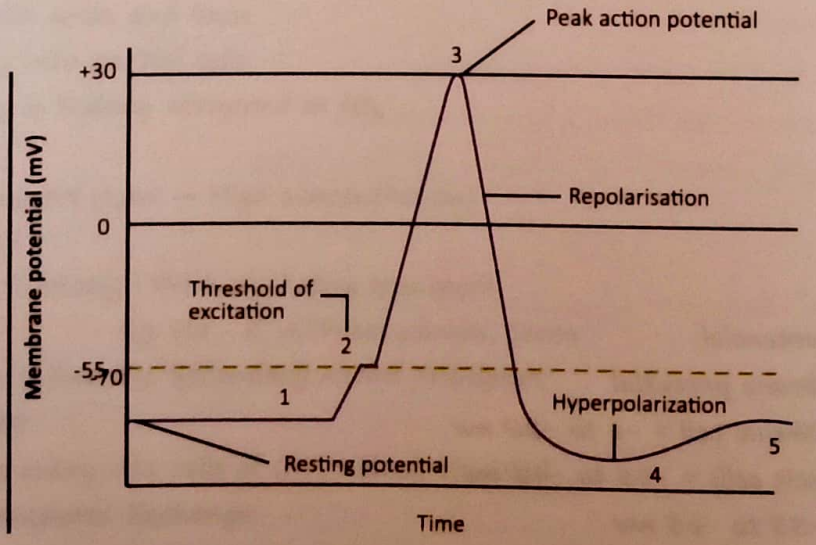
- Concentration gradient of individual ions
- Membrane permeability

$$EMF = \pm 61 \times \log \left[\frac{(C\,Na^+ \times P\,Na^+) + (C\,K^+ \times P\,K^+) + (C\,cl^- \times P\,cl^-)}{(C\,Na^+ \times P\,Na^+) + (C\,K^+ \times P\,K^+) + (C\,cl^- \times P\,cl^-)} \right]$$

→ **Acc to GHK equation:-**

Membrane = -86 mv(by Diffusion of 3 ions) and Na^+ - K pump contributed - 4 mv

Action potential

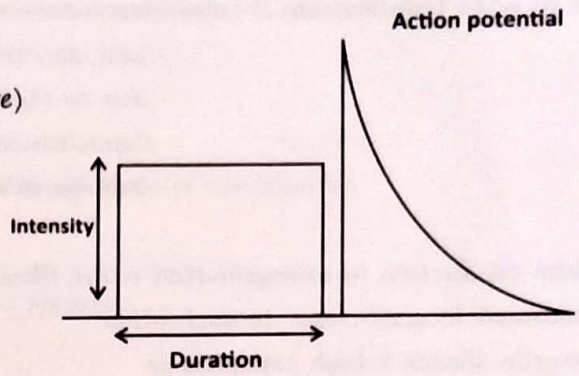


Stimulus

→ Two properties – Intensity and Duration

→ Two Best stimuli to excite a tissue are: -

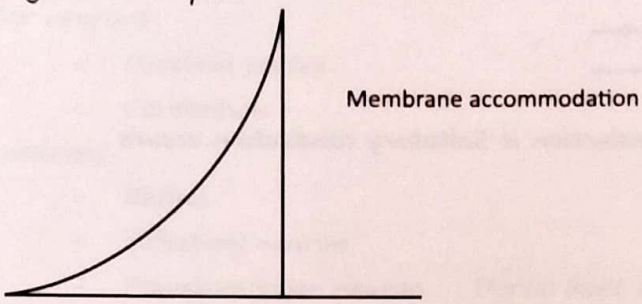
- Rectangular pulse (Best stimuli to excite nerve)
- Exponential pulse.



→ Slowly rising stimulus Intensity

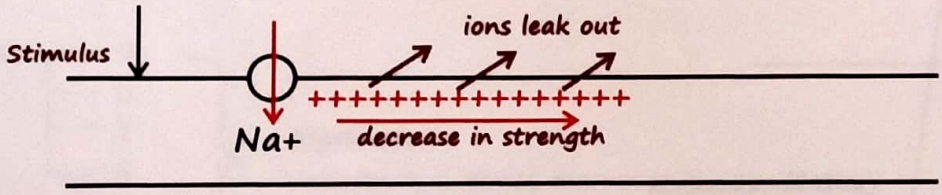
→ membrane accommodation

→ Na^+ channel open slowly – enough number of Na^+ channels will not be available at one time to generate a spike.

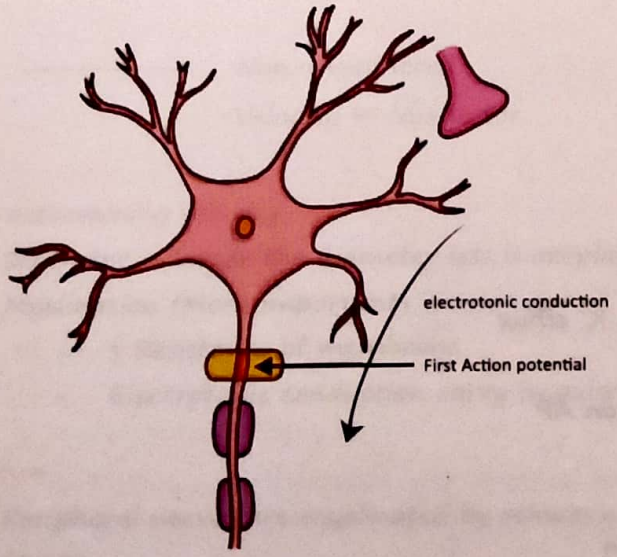


Impulse transmission

1. **Electrotonic conduction** – direct, passive spread of charges from point of entry
   - Detrimental (strength decreases)
   - Ions leak out due to membrane capacitance ©

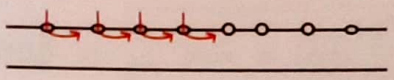


- By 10 mm length – all ions leak out → Electrotonic Conduction stops
- It happens from Dendrites to axon hillock.



→ First action potential will be generated at axon hillock (lower threshold for generating AP)
→ Node to node transmission – also Electronic conduction
- Less decremental
- due to Myelin sheath which ↑ Resistance, ↓ Capacitance
- leakage of charges will be less

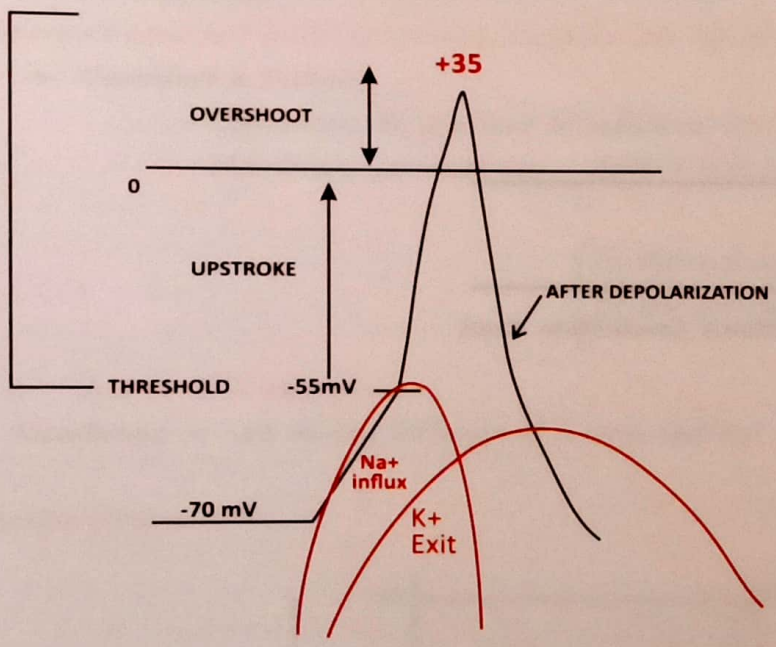
→ Impulse conduction in unmyelinated nerve fibres – by local currents
→ Na channels located closer to each other
→ No myelin sheath = high capacitance



→ In myelinated nerve fiber, node to node conduction ie Saltatory conduction occurs
→ AP occurs only at nodes of Ranvier
→ Consumes less ATPs and it is Faster

Phases Of Action Potential

→ Depolarization (inside becomes positive) – Na^+ influx
Repolarization (Inside becomes negative) – (K^+ efflux)



→ After depolarization – Slow down of Repolarization
- because of decrease in K^+ efflux
→ Hyperpolarization – excess K^+ leaves

Effect of changes in ionic composition on AP

→ **ECF - Na^+**

In Hyponatremia -

- Conc. Gradient for Na^+ narrowed; influx of less sodium
- Amplitude of action potential decrease
  → K^+

In Hypokalemia

- Hyperpolarization: Conc. Gradient for K^+ widened and excess K^+ go out
  → Ca^{++}

In Hypocalcemia (tetany):

- Na^+ channels become unstable
- Faint stimulus → no. of impulses to muscles – sustained state of contraction

NERVE

→ Structural and functional unit of Nervous system – Neuron

Types of Neurons

→ Multipolar neurons
- Cerebral cortex
- Cerebellum

→ Bipolar neurons
- Retina
- Olfactory neuron
- Pseudounipolar neuron - Dorsal Root Ganglion

→ Anaxonal neuron
- Amacrine cells in retina
- Post-ganglionic parasympathetic

Classification of Nerve fibres

A — α, β, γ, δ
B

Myelinated
Velocity ∝ 6 times diameter (Hursh factor)

C ⟶ **Non-myelinated**
Velocity $\propto \sqrt{\text{diameter}}$

Factors determining velocity

→ Diameter – larger the diameter less is axoplasmic resistance
→ Myelination (More important)
- ↑ Resistance of membrane
- Electrotonic conduction carry impulse faster

Myelination

→ Peripheral nerves are myelinated by schwann cells – Many Schwann cells myelinate 1 schwann cell (20:1)
→ CNS myelination is by Oligodendrocyte (1:20) - 1 oligodendrocyte myelinate 20 axons

Erlanger and Gasser classification of Nerve fibers

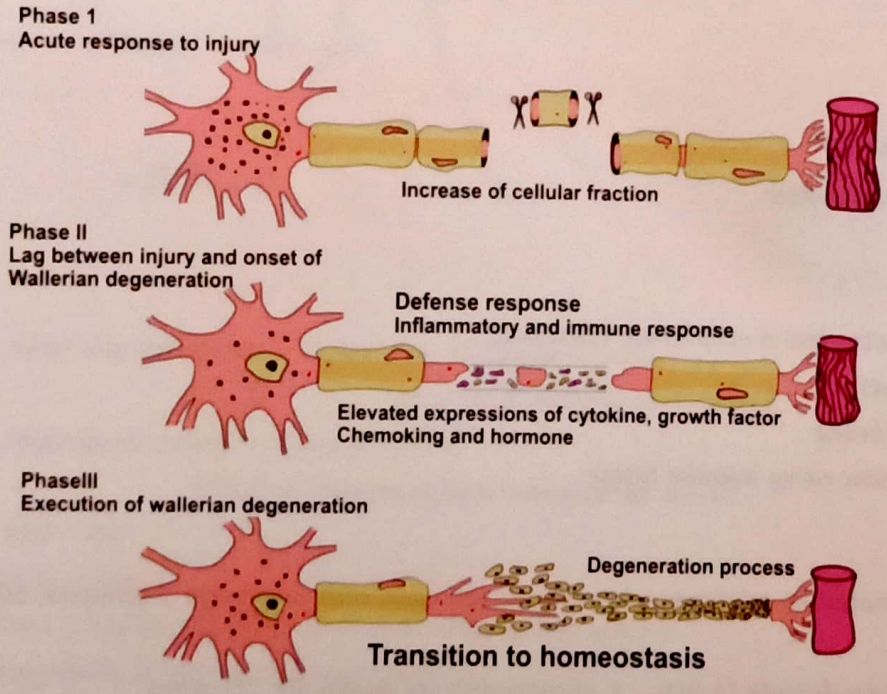
Aα	myelinated	carry proprioception, α - motor neuron	fastest
Aβ		Touch, pressure	
Aγ		γ - motor neuron	
Aδ		Fast pain and temperature	
B		Preganglionic autonomic (both sympathetic and parasympathetic	
C	unmyelinated	Somatic → slow pain Autonomic → Post -ganglionic sympathetic	slowest

Numerical Classification (Only Sensory Fibres)

Ia – proprioception → dynamic stretch from muscle spindle 1 affected
Ib –starts from golgi tendon organ; detects tension in muscle
II –Secondary afferent, static stretch
III – Touch, Pressure
IV – Pain, Temperature

Injury To Nerve Fibres

A → most susceptible to Pressure
B → most susceptible to hypoxia
C → most susceptible to local Anesthetics
Wallerian degeneration – changes seen in distal segment after transection



Chronology of Events After Transection

24 – 48 Hrs → Chromatolysis (1st Change in Nerve Trunk)
By 6th Day → Axonal degeneration (1st Change in Wallerian Degeneration)
10th day → Myelin degeneration
15th day → Sprouting from proximal end
→ Schwann Cell Proliferation

→ Repair will complete in about 80 days after transection.

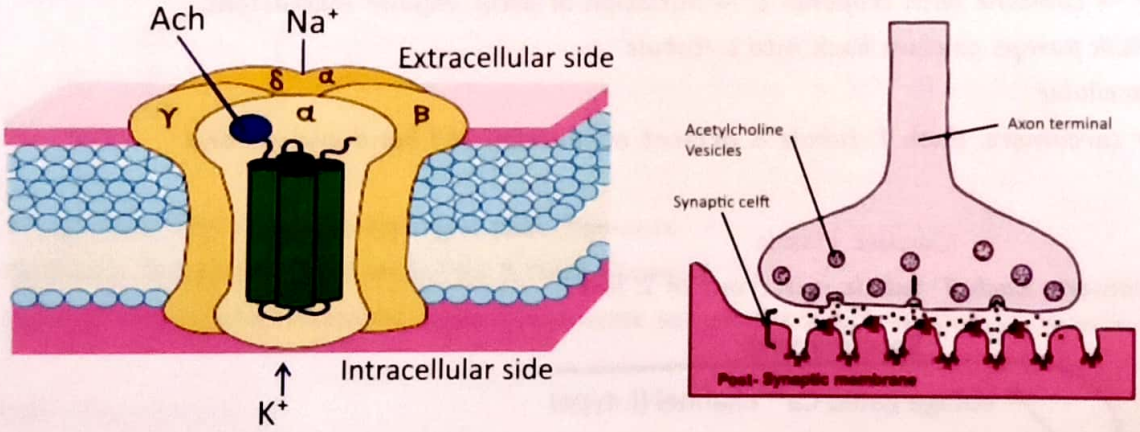
Muscle

- Neuromuscular junction
- EC Coupling
- sarcomere

Neuromuscular Junction

→ **Synthesis of Acetylcholine Vesicle**
  - Ach→ Synthesized locally in nerve terminal
  - Vesicle → synthesized from nerve cell body

Acetylcholine Binds to Receptor → Channel opens → Same channel allows Na^+ influx, K^+ efflux → At −90mV (RMP) Na^+ influx predominate →Results in EPP (End Plate Potential)



→ 1 Impulse = 60 vesicles released (Each vesicle = 10,000 molecules) → End Plate Potential EPP = 40mV → Action potential → Muscle contraction

Autoimmune Diseases

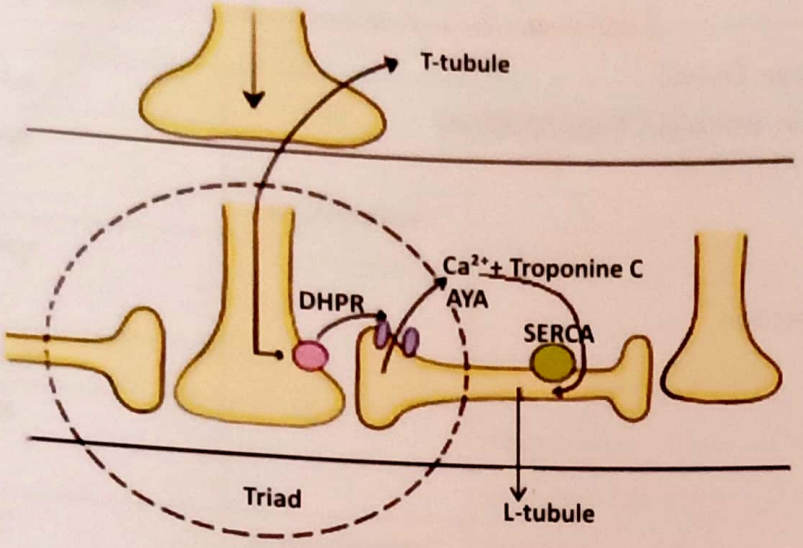
→ **Related to Ca^{2+}** → Lambert – Eaton Syndrome - with repeated muscle contraction – strength of contraction improves since, Ca^{2+} is accumulating.

→ **Related To Nicotinic Ach Receptor** → Myasthenia gravis – with repeated muscle contraction – Strength of contraction worsens.

Excitation – Contraction Coupling

→ Ca^{2+} is the coupling agent between electrical excitation and mechanical contraction of muscle.

→ Occurs in sarcotubular system of the muscle.



Skeletal muscle

- **Skeletal muscle** → Two T-tubules /sarcomere
- **Membrane of T – Tubule** → DHPR (Voltage Sensitive Ca^{2+} Channel)
- **Membrane of L – Tubule** → RYR (Ca^{2+} Release Channel)

→ Nerve passes on signal to T-Tubule → DHPR sense it → mechanically interact with RYR → Ca^{2+} released into sarcoplasm → combine with troponin C → initiation of actin-myosin interaction.

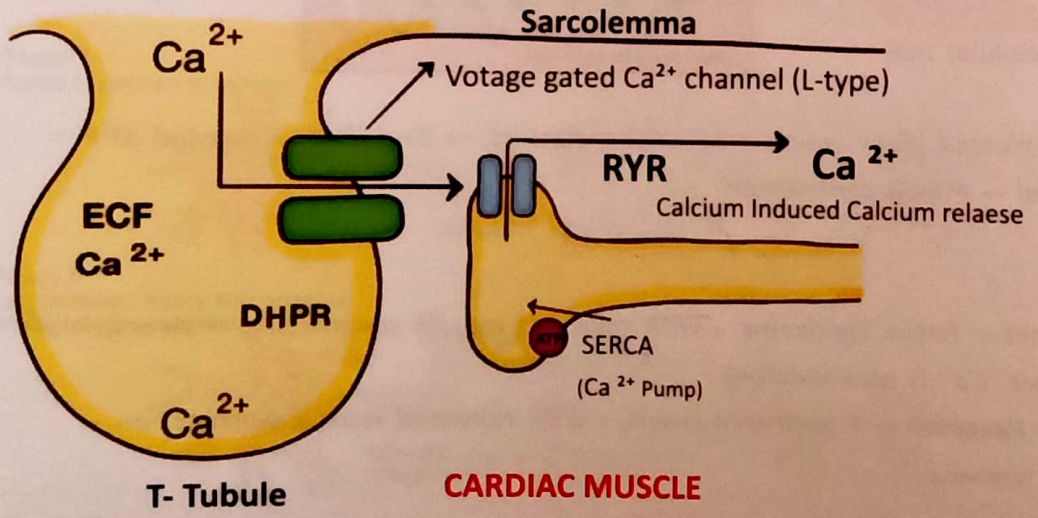
→ **Relaxation** → SERCA pumps calcium back into L-tubule

Note : all Ca^{++} is intracellular

→ Two T-tubules per sarcomere. Each T-tubule is present at junction at I band and A band.

Cardiac Muscle

→ 1 T-tubule / Sarcomere. Each T-tubule is in front of Z line

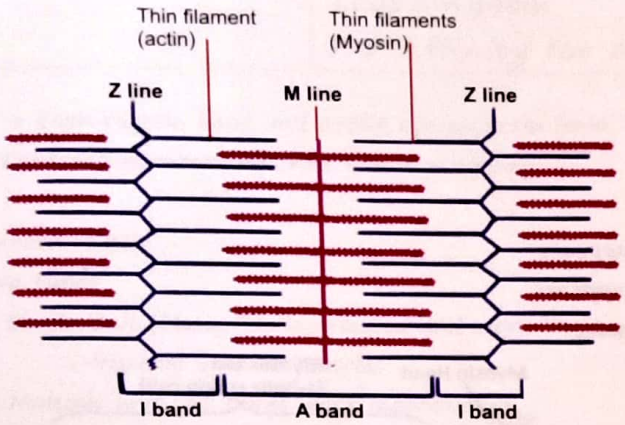


→ T-Tubule is storehouse of Ca^{2+}

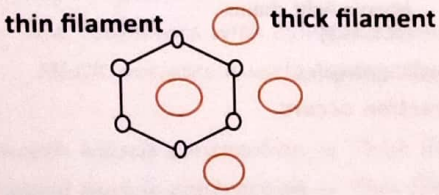
- Depolarization → DHPR → ECF Ca^{2+} enters via L type Ca channel → cause further Ca^{2+} release from RYR, known as **Calcium Induced Calcium Release**. Hence, change in ECF calcium affects cardiac contractility not the skeletal muscle contractility

Note → Calcium Channel Blockers →DHPs → Blocks DHPR of cardiac muscles and smooth muscles, not of skeletal muscle.

SARCOMERE



Z – Line Cross Section – Hexagonal



→ 1 thick filament is surrounded by 6 thin filaments.
→ Each thin filament – surrounded by 3 thick filament
→ Ratio of thin to thick filament in skeletal muscle sarcomere = 2:1; in smooth muscle it is 15:1.

Length of sarcomere

→ Initial / Resting Length of sarcomere → 2.0 μ (Li) distance between two successive Z-line
→ Optimum Length – (Lo) → 2.2μ (LO) (Starling's Law is applicable)

Note:- at Lo muscle contraction is strongest due to Frank starling's law (greater the initial length - strongest is the contraction) beyond this length (Lo) the sarcomere will become weak and strength of contraction decreases.

→ L_{Max} → 3.65μ (Do not produce any contraction)

TITIN

→ Largest known human protein
→ Anchored to Z line and connects Z–Line with M–Line.
Function → Alignment of thick filament in sarcomere.
- Defective Titin → Limb girdle muscular dystrophy.
→ 1 Sarcomere = 1 Full A–Band + 2 half I- bands
→ Centre of 'A' band → 'H' – zone

→ Centre of 'H' – zone → 'M' line

→ Dark 'M' line + adjoining light areas – Pseudo H Zones

Changes During Muscle Contraction

→ Sarcomere Shortening

- A-Band → Remain unchanged
- I-Band → Shortens
- H-Zone → Disappears
- M-Line → Become prominent

Extra:-

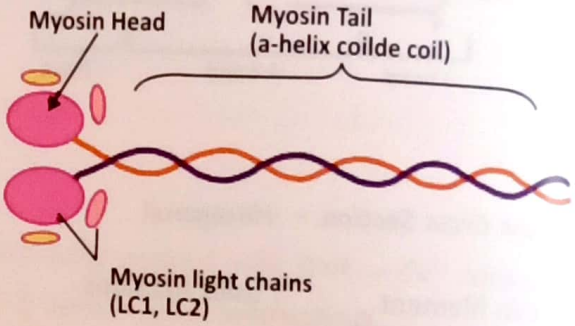
At 1.5μ contracted length of sarcomere → Cm band appears

At 1.25μ contracted length of sarcomere → Cz band appears

Thick Filament → 1 thick filament = 500 myosin molecule

→ Each Myosin → 2 heavy chains + 4 light chains

→ Head Of Myosin → ATPase enzyme



Thin Filament

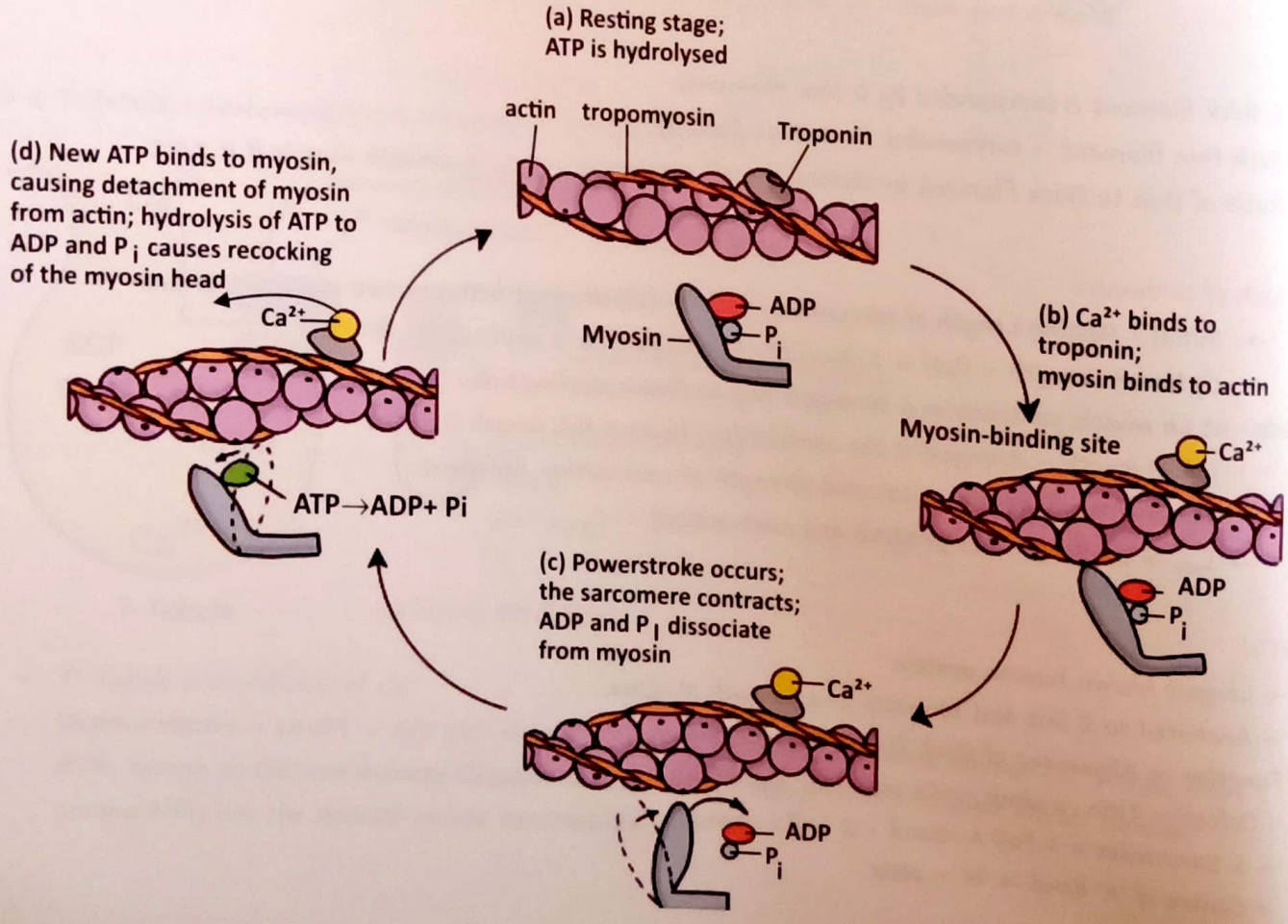
Actin : Troponin : Tropomyosin

7 : 1 : 1

Actin

→ Have active sites and active sites covered by troponin- tropomyosin complex

→ Ca^{2+} binds troponin – site is uncovered and actin – myosin interaction occurs.



Troponin types	
Troponin	C → Affinity for Calciu T → Affinity for Tropomyosin I → Affinity for Actin

→ Each myosin head and active site on actin form – cross bridge

→ Contraction occurs by cross – bridge cycling

Smooth Muscle

Two Types

→ Single Unit (Many Fibres grouped and work like single unit)

:-Visceral Smooth Muscles

→ Multiple unit (All fibres work individually)

:- Arrector Pili – Ciliary Body Muscles

- In smooth muscles No Z – line; Instead dense bodies present
- Thin: Thick Filaments = 15:1
- No Troponin C
- Ca^{2+} combines with calmodulin and activation of MLCK (Myosin Light Chain Kinase)
- MLCK initiates muscle contraction.

Note

→ Smooth muscle contraction → Thick filament regulated contraction

→ Skeletal muscle contraction → Thin filament regulated contraction

Latch Bridge→ After certain percentage of cross – bridge cycling no further cross – bridge cycling occurs.

Advantage → Lesser ATP consumption

→ Sustained and tonic contraction

CVS

- Conduction system
- Cardiac cycle
- Cardiac output
- Circulation

Introduction

→ Heart muscle works as Syncytium due to gap junctions works as 2 syncytia – Both Atria working as one syncytium and ventricles working as another syncytium.

→ Intercalated discs in the Heart provide electromechanical tethering to fibers.

Innervation of Heart

→ Sympathetic fibers are predominantly epicardial so they mainly controls contractility

→ Parasympathetic vagal fibers are predominantly endocardial in Distribution therefore since where in conduction system in endocardium – vagus mainly controls HR

Note: - Right vagus innervates SA node.

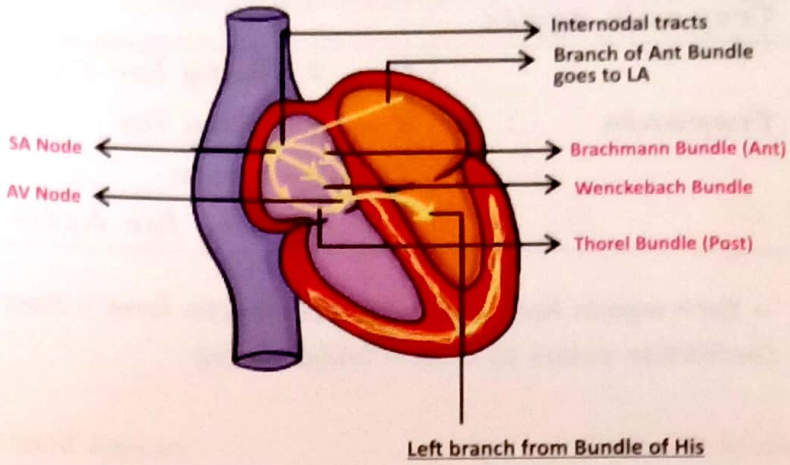
Left vagus Innervates AV node.

Conduction system of Heart

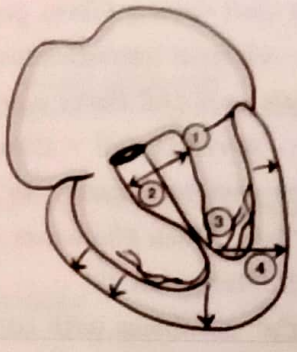
Right atrium contracts ahead of left atrium

SA node → **Via 3 inter nodal tracts** → **AV node**

- Bachman Bundle (anterior) – one brach goes to left atrium
- Wenckebach bundle (middle)
- Thorel's bundle (posterior)



- Impulse From AV node goes to Bundle of His
- It gives off left branch and bundle itself continues as right branch
- Impulse enters the left branch first then through septum it goes to right then comes in branches towards the Apex.
- This left to right spread electrical mechanical Activity is responsible for Q wave on ECG.
- from Apex to base (Endocardium to Epicardium) impulse travels via Purkinje fibres



Note: - Last part to depolarize – Epicardium of base of Heart (left ventricle)

→ From start of impulse 0.00 sec at SA node

- **Right Ventricle** Completely depolarize in 0.22 sec
- Left ventricle in (0.23 sec)

→Because the muscle Mass of left ventricle is more and it takes slightly more time to depolarize.

Repolarization(Reverse Occurs)

Base → Apex

So last part to repolarize – Apical Endocardium

Note: - Parts last to depolarized: -

→ Epicardium of base of LV

→ Uppermost part of septum

→ Pulmonary conus

Action potential of heart: -

Slow Response/ slowly depolarizing	Fast Response/ rapidly depolarizing
SA node, AV node - RMP = -55 to -60 mV - Slow and spontaneous depolarization but rapid recovery - Rhythmicity is faster	**Purkinje fibers, Ventricular fibers** - RMP = -90 mV - Fast depolarization but slow and prolonged repolarization

Note: - SA node acts as pacemaker because of slow but spontaneous depolarization threshold stimuli after every repolarization that provides Automaticity.

Automaticity is provided by AV node also but recovery after every impulse is fastest in SA node.

Note: - In every part of Heart, they have their own type of Rhythm ability but due to faster Rhythmicity of SA node – all the muscle follows the Rhythm of SA node
But in case of some problem infarct damage to conducting system: - The individual rhythmicity acts along with Rhythmicity of SA node. And causes problem in condition.

Rate of depolarization: -

- → It determines the impulse conduction speed.
- → SA node → 0.05-0.1 m/sec
- → AV node → 0.05 – 0.1 m/sec
- → HIS bundle → 1 m/sec
- → Purkinje fibers → 1.5 - 4 m/sec

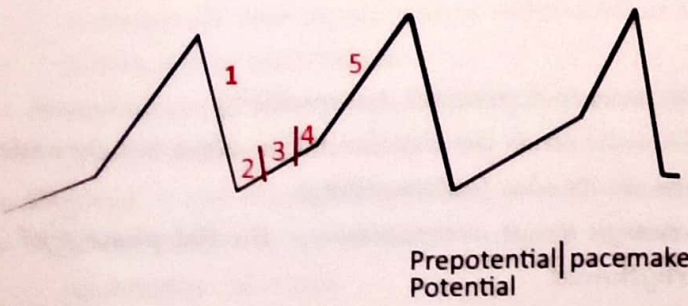
Note: - In Purkinje fibers there are large diameter fibers and more gap junctions.
Slowest conducting part in Heart = AV node, because of slowly depolarizing and ↓↓ no of gap junction out all diameter fibers

Rate of repolarization: -

- → It determines Natural rhythmicity / excitability of that part
- → SA node — 80-100/ min (N-70-80 due to vagal inhibitory effect)
- → AV node — 60/min
- → Purkinje fibers — 15-40/min

Ionic basis of AP's in Heart
SA /AV node – slow Response

SA/AV node __ Slow Response



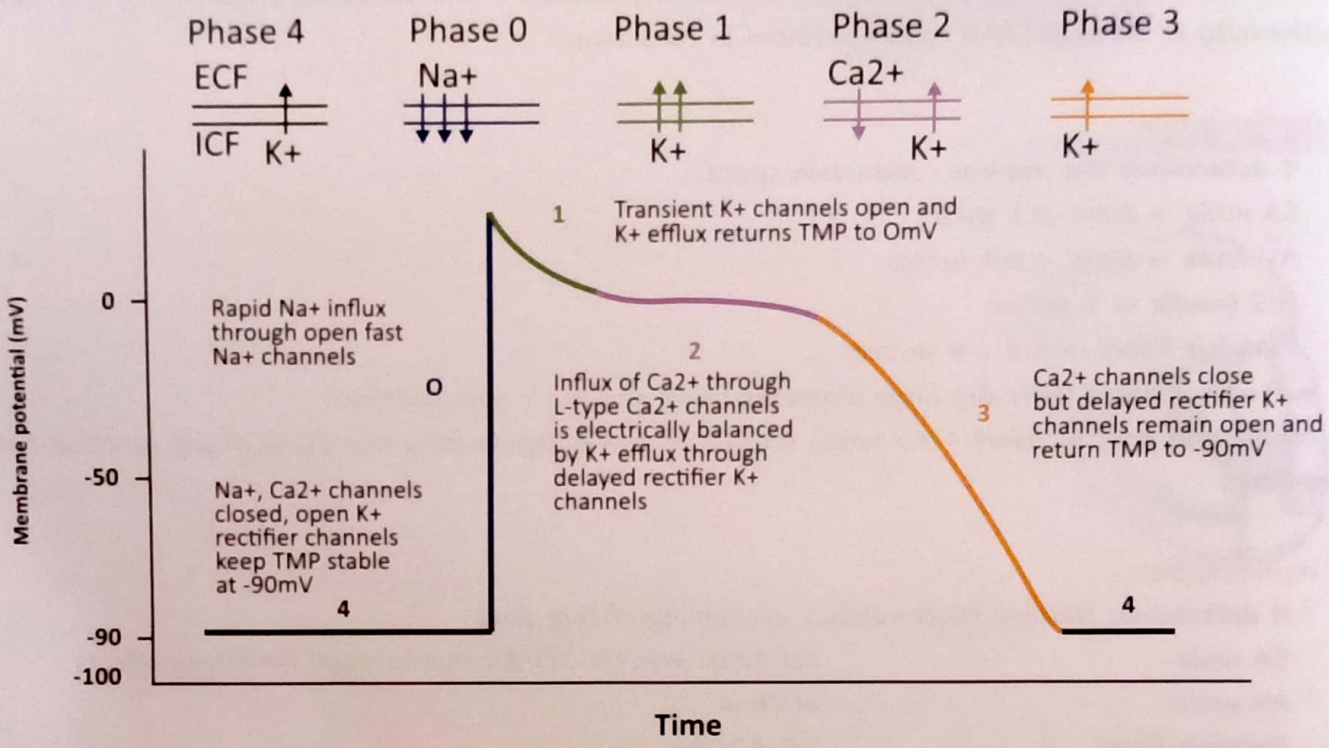
1. Due to K^+ exit.
2. Due to K^+ exit stops and K^+ starts accumulating inside the membrane
3. Due to influx of Na due to "Funny channels" → HCN: – Hyperpolarization activated cyclic Nucleotide gated channels
4. Depolarization reaches threshold → occurs by Ca channels acting through "T channels"
5. Depolarization above threshold → it is completed by influx of "Ca" through " L channels"

K → Na → Ca → Ca

Note:- Largest current of depolarization in SA node is by "Ca" in SA node.

→ Largest current of depolarization by Purkinje fibers is by "Na"

Action potential of cardiac muscles



1. **Rapid upstroke**: - It is done by fast Na channels
2. **Early repolarization**: -due to K^+ efflux that is just started.
3. **Plateau phase**: - due to slow influx of Ca through Ca channels
4. **Delayed repolarization**: - due to K^+ exit.
5. Resting membrane potential.

Note: - Phase (4°) is flat in Purkinje but steep in SA node because it provides Automaticity.

→ Purkinje fibers can depolarize again only when SA node sends the depolarization wave but Sa node can be depolarized again at end of Repolarization on its own (automaticity)

→ But in conditions such as Ischemia, Hypoxia. Adrenergic drugs, tetrodotoxin – the flat phase (4) of Purkinje fibers can become sleep and causes Arrhythmias.

Significance of Plateau phase (slow La channel)

→ Long AP duration (200-300 msec)

→ Long recovery time/ long repolarization

→ Long refractory period – so Heart cannot tetanized due to high frequency stimulation.

Cardiac Cycle

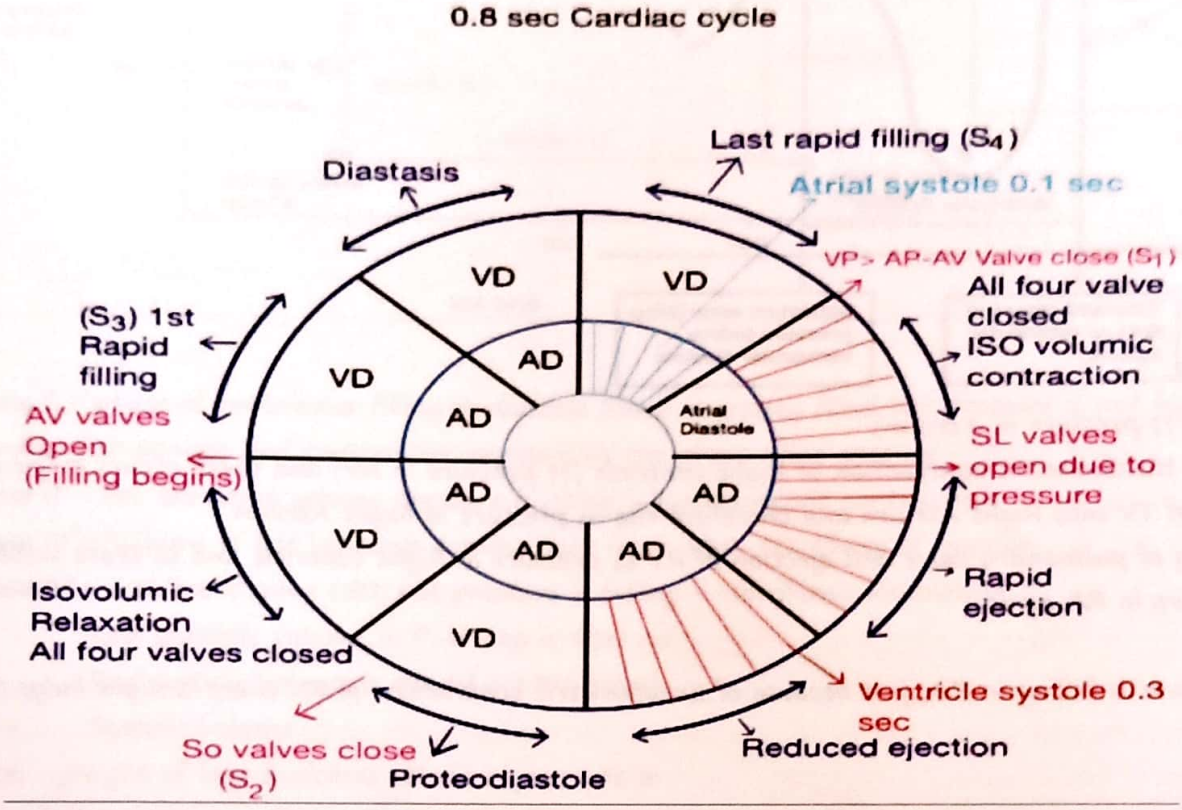
Events that occur in one heart beat

→ Duration – 0.8 sec

→ Events in cardiac cycle

Atrial events	Ventricle events
Systole 0.1 sec	Systole 0.3 sec
Diastole 0.7 sec	Diastole 0.5 sec

Note: - At higher HR, cardia cycle duration will be shortened but diastolic function suffers more.



→ Atrial systole is further divided into two parts.

Dynamic Atrial systole 0.05 sec. – here majority of fibers are contracting and most of blood is pumped from Atria to Ventricles

Adynamic Atrial Systole 0.05 sec

→ For most part of ventricular diastole – Atria are also in Diastole and only last part of the VD corresponds with Atrial systole →75-80% of Ventricular filling is passive and only 20-25% is by Active Atrial contraction.

→ **Protodiastolic** – first part of Ventricular diastole here the sudden change of blood flow occurs. It ends by S_2 production.

→ Diastasis – not much filling in this phase – ventricles Atria are in diastole.

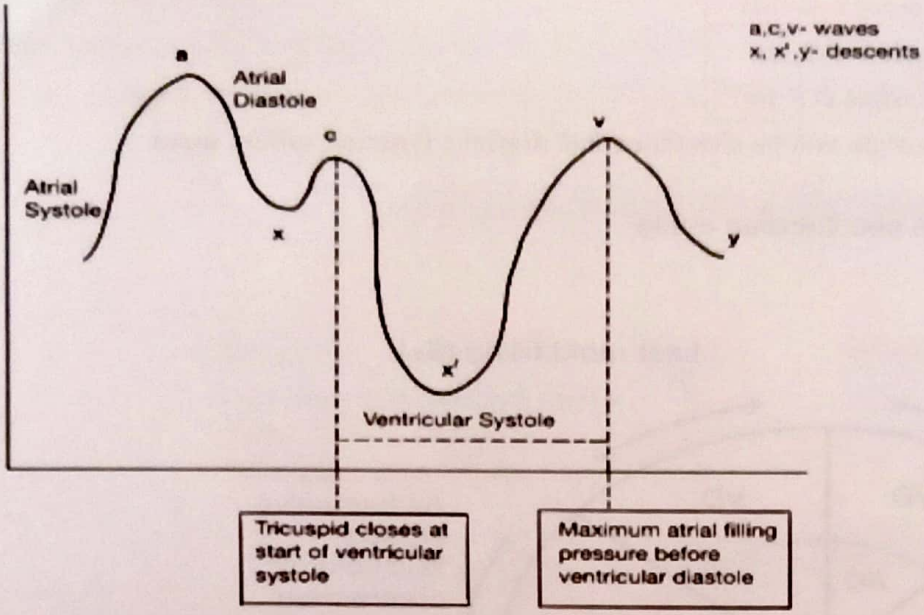
→ S_4 is also known as atrial sound →due to turbulence created by blood passing into ventricles by contraction of Atria.

Pressure changes in cardiac cycle

Atrial pressure changes:

→ Right Atrial pressure – JVP [(0-5 cm of H_2O (+/-5)]. It increases with expiration and decreases with inspiration.

→ Left Atrial pressure – PCWP (5mm. Hg 5-8 cm H_2O)



(a) Atrial systole (↑↑ pressure in Atrium)

(c) It is caused by Isovolumetric contraction of Right ventricle (↑↑ pressure in RV) and there occurs bulging backwards of TV into Right Atrium and therefore rise in pressure of Right Atrium.

(x) due to opening of pulmonary valve and ejection of RV ↓↓ pressure in Right ventricle and so there would be ↓↓ pressure in RA again.

Note: - The pressure is falling in RA, just because of Isovolumetric contraction of RV there is slight bulge (c) in graph.

(v) → Venous blood accumulates because of Isovolumetric relaxation of ventricles

→ Pulmonary close and Tricuspid valve is yet to open so therefore there occurs accumulation of blood coming from periphery into Ⓡ Atrium

(Y) downslope→ Indicates Right ventricular filling due to opening of Tricuspid valve.

Note: - In cardiac Tamponade and constrictive pericarditis – Y downslope is abnormal because it indicates ventricular filing and in cardiac T and C. Pericarditis that is Hampered.

- Normally (V)wave is larger in LA compared to RA because left atrium receives 1-2% extra blood compared to Right Atrium due to blood from bronchial circulation (Bronchial vein joins pulmonary vein)

a – Atrial contraction

x – Atrial Relaxation

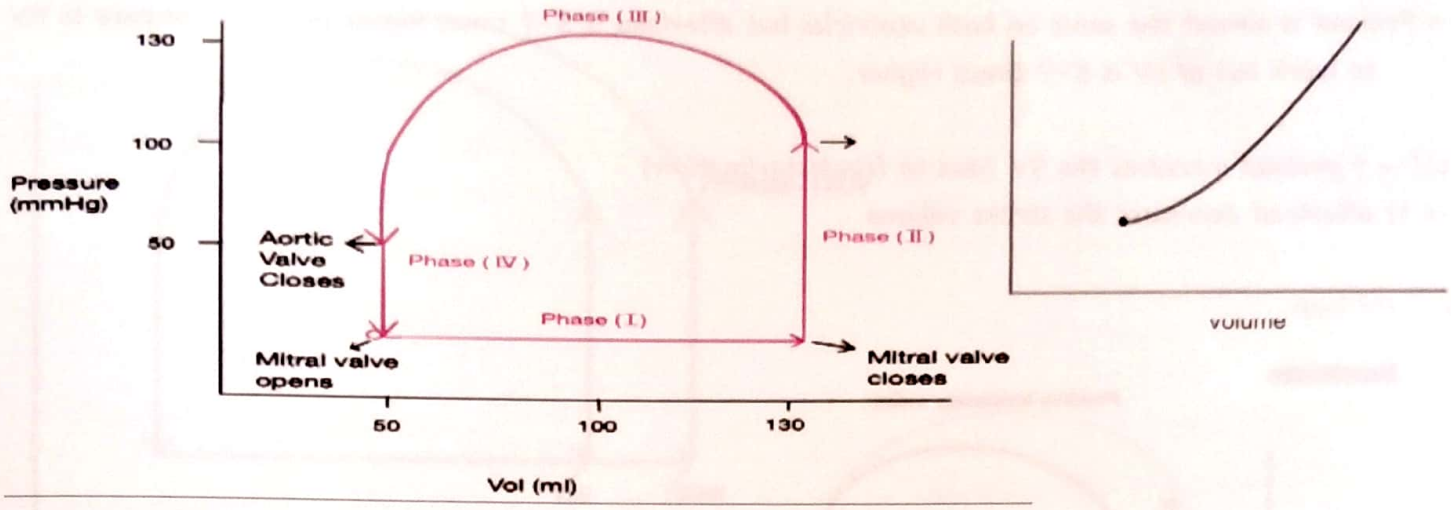
c – Bulging of tricuspid value with Ventricular contraction.

x – Downward movement of Tricuspid value with ventricular contraction

v – Passive Atrial filling

y – Atrial emptying with opening of the Tricuspid value.

Changes in left ventricle



Phase I – phase of ventricular filling in diastole Blood is getting filled but pressure is not increasing cardiac Tamponade and constrictive pericarditis the phase I line goes up

Phase II – For the same volume pressure is rising – Isovolumetric contraction.

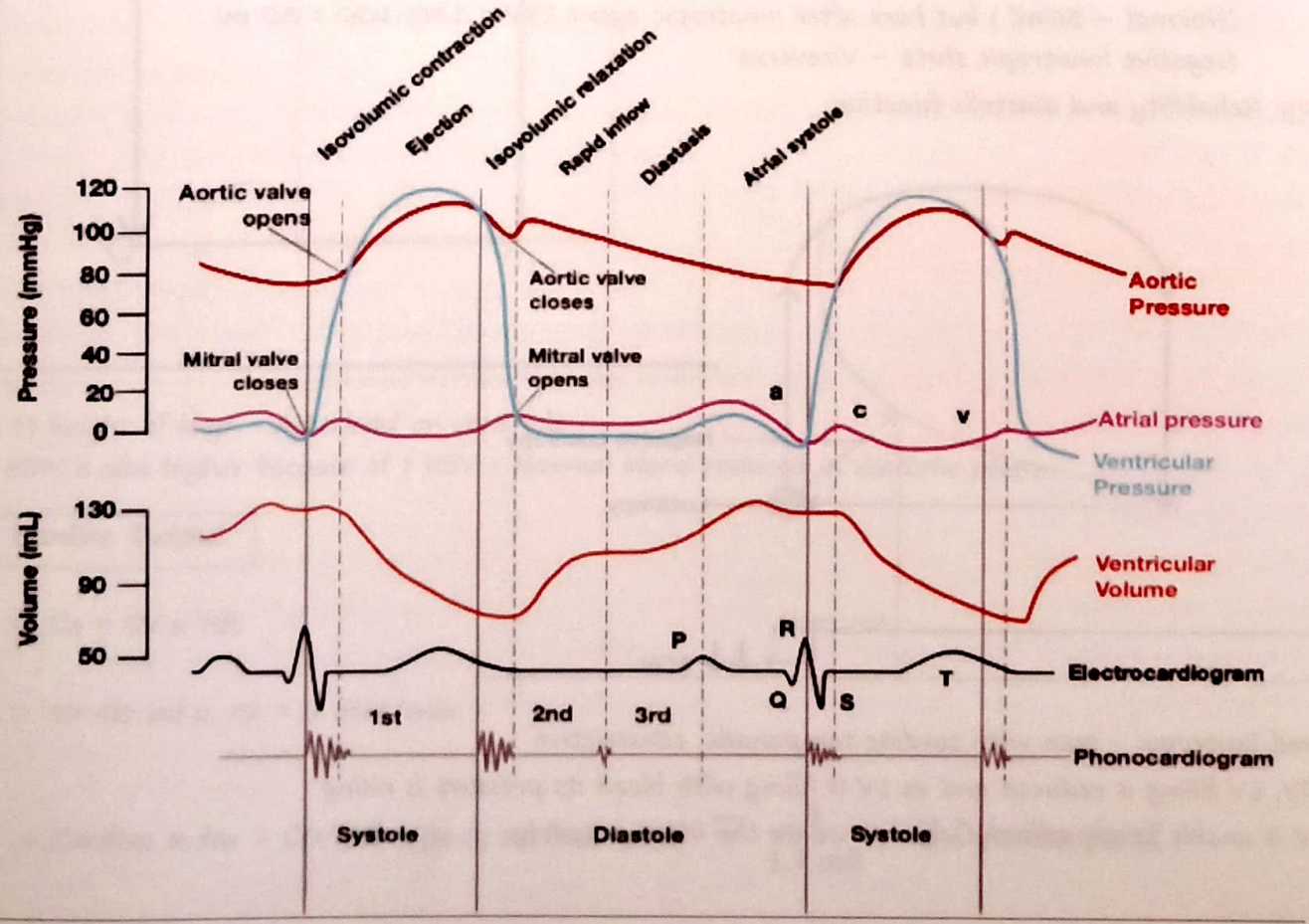
Phase III – Volume of left ventricle coming back from 130-50. Phase of ejection

Phase IV – Volume is same (50) but pressure is falling – Isovolumic Relaxation

- End diastolic volume in P-V loop is 130 ml
- End systolic volume is 50 ml = 130-80ml
- Systolic volume

Note: - Height of loop indicates afterload pressure in LV and that indicates afterload on ventricle.

- EDV indicates preload on LV

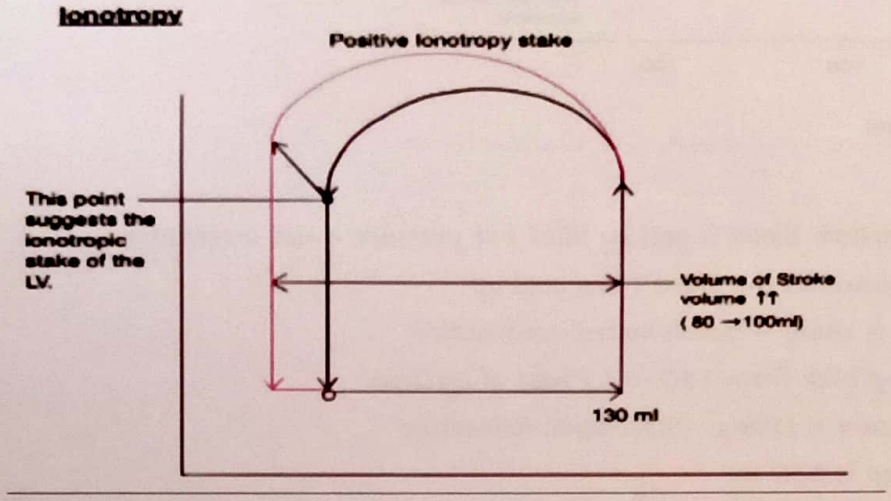


Comparison between LV and RV

→ Preload is almost the same on both ventricles but afterload is 5-7 times higher in LV as compare to RV so work out of LV is 5-7 times Higher.

LV → ↑ preload increases the SV. (due to front starling low)
→ ↑↑ afterload decreases the stroke volume

LV – PV loop

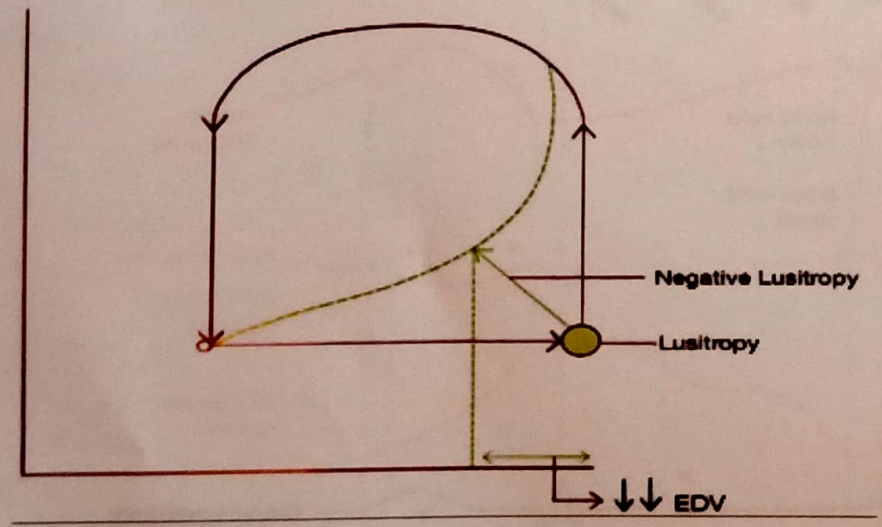


Positive inotropic state

→ Starting form same end diastolic volume/ length the ventricles are contracting stronger and more amount of blood ejected (↑SV)
Note: - Frank starling low is not applicable here.

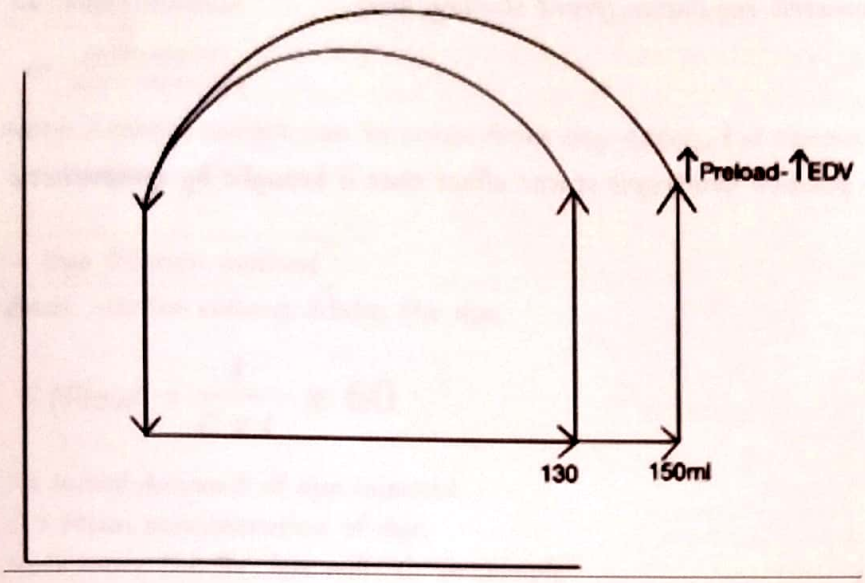
→ The fallout of Ionotropic state is ↓↓ ESV.
(Normal – 50ml) but here after ionotropic agent ESV = 130-100 = 30 ml
Negative Ionotropic state – Viceversa

Lusitropy: Reliability and diastolic function



Altered lusitropy: - seen with cardiac tamponade, constrictive
↓↓ EDV, LV filling is reduced and as LV is filling with blood its pressure is rising
→ LV is unable to expand and accommodate the blood properly.

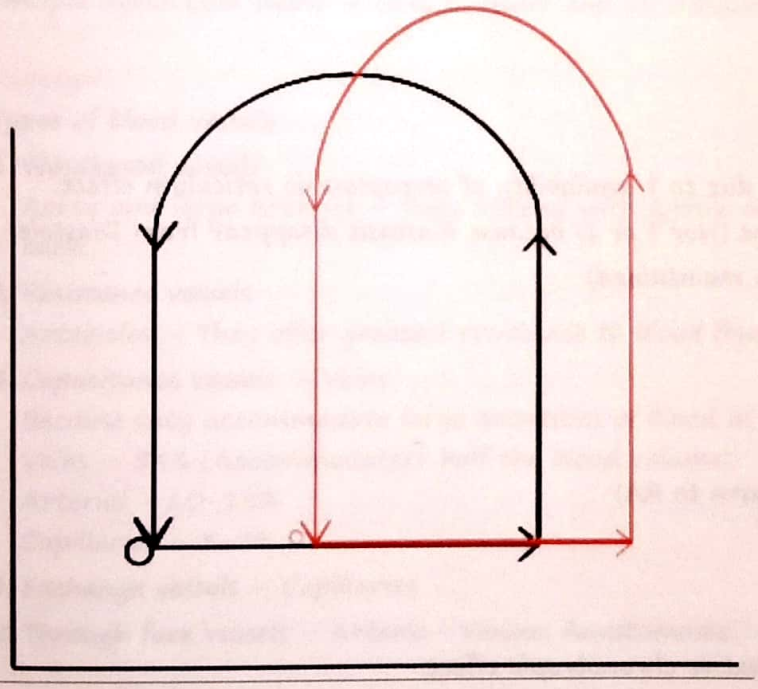
↑ Preload → Heart contracts stranger – SV is Higher (LV pressure is higher)



→ Out of 150ml of EDV – 100ml is ejected out (↑SV) = 50 ml ESV remains same.

→ ESV remains same.

↑ Afterload → ↓↓ stroke volume and ↑↑ ESV



→ ↑↑ height of loop – Afterload on ventricle

→ EDV is also higher because of ↑ ESV + Normal blood reduced in diastolic phase.

Cardiac Output

→ Co = SV x HR

= 70-90 ml x 72 = 5 litre/min

→ Cardiac Index = CO/BSA (Body surface Area) $= \frac{5}{1.7\ m2} = 3\ l\ /min\ /m2$

Factors determining CO

1. SV – depends on (I) intrinsic / Heterometric regulation (front starling low)
   SV ∝ EDV ∝ Venous Return
   ∝ EDL
   ∝ Preload
2. Extrinsic / Homeometric regulation – positive ionotropic state/ effect that is brought by sympathetic discharge, catecholamines digitalis

Two indices relaed to stroke volume

→ EF(Ejection fraction)

$$EF = \frac{SV}{EDV} x\ 100 = 60 - 65\%\ Normal$$

EF ↓ in LV failure.

→ **LVSF** (Left ventricle shortening fraction)

- During systole how much shortening occurs.

$$LVSF = \frac{(LVEDL - LVESL)}{LVEDL} x\ 100$$

(Left ventricle end Diastolic length)

= 40% is normal value (↓ in LVF)

2. HR

→ 72-130 BPM →↑ HR and ↑ SV by stair case due to ↑ availability of sarcoplasmic reticulum effect.

→ 130-160 BPM → ↑ HR and SV remains same (Nor ↑ or ↓) because diastasis disappear from Diastole.

→ 160 (Highest ventricular rate at which CO is maintained)

Note: - HR MAX = 220 Age.

Imp points

→ **Bain Bridge Reflex:**

- IV saline (or any factor that ↑ the venous return to RA)
  ↓
  Sudden ↑↑ HR and therefore ↑ CO

→ **Chronotropic effect**

- Sympathetic are positive and vagus has negative chronotropic effect.

→ **Dromotropic effect**

- Effect on Impulse conduction speed

→ **Ionotropic effect**

- Effect on contractility

→ **Bathmotropic effect**

- General excitability effect on Heart

→ **Lusitropic effect**

- Affect on Relaxibulity on diastolic function.

Methods of measurement of CO

→ Fick's method

$$CO = \frac{O2\ consumption}{A\text{-}V\ O2\ difference}$$

Note: Arterial sample can be taken from any Artery but venous sample should be collected from pulmonary artery.

→ Dye Dilution method

Basis: -stroke volume dilutes the dye.

$$F\ (Flow) = \frac{I}{C\ x\ t}\ x\ 60$$

I = Initial Amount of dye Injected
C = Mean concentration of dye.
Note more the SV, less will "C" in sample
t = Time in sec at which dye disappear for first time on Arterial side.

→Thermodilution Method

Principle Inject Cold saline → Goes to heart and SV dissipates the temperature.

Circulation

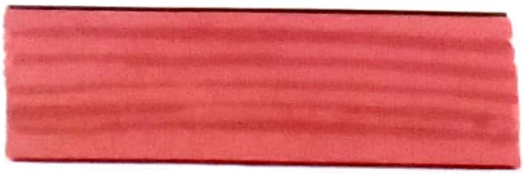
Types of blood vessels

1. **Windkessel vessels**
   Aorta and large Arteries – They distend with systole and when Heart goes back to diastole they recoil back.
2. **Resistance vessels**
   Arterioles – They offer greatest resistance to blood flout and they cause greatest drop in pressure.
3. **Capacitance vessels**: - Veins
   Because they accommodate large quantities of blood at any given time.
   Veins – 54% (Accommodates> half the blood volume)
   Arterial - 10-15%
   Capillaries – 5-8%
4. **Exchange vessels** – Capillaries
5. **Through fare vessels** – Arterio– Venous Anastomoses.

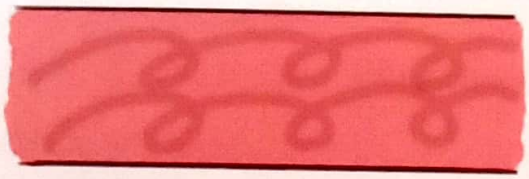
Blood flow to organs

→ **Highest blood flow** –
- Liver 25-27% (measured by BSP)
- Kidney 22-25% (measured by PAH)

→ **Highest blood flow 100 gm/min**
- If tissue asked – carotid body (2000ml per 100 gm/ min
- If organ asked - kidney



Normal blood flow
↓
Laminar/Silent flow



AV currents generated in blood
↓
Turbulent blood flow and it produces sound

→ Probability of producing Turbulence is given by the Reynold's number

Reynold's Number: - Re

Re < 2000 = Laminar

Re > 3000 = Turbulent

$$Re \ \frac{Vdp}{\mu}$$

V = Velocity,
d = Diameter
P = density of blood
μ = viscosity of blood

Blood pressure

1. Determinants of Arterial Blood pressure

Ohm' low – $Q = \frac{\Delta P}{R}$

Q = flow /Co

$CO = \frac{BP}{R}$ so, BP = COX Total peripheral Resistance (R)

→Vasoconstriction – R ↑↑ and vasodilation R ↓↓

2. Types of BP

- **Systolic BP** – Indicates force of Contraction of Heart
- **Diastolic BP** – Indicates peripheral resistance

Note: - Maximum peripheral resistance (> Half) is contributed by skeletal Muscle contraction.

→ **Pulse pressure** = (SBP – DBP) → It indicates the stroke volume.

→ **MAP (mean arterial pressure)** – DBP + 1/3rd of pulse pressure.

Note: - MAP does not come out as accurate arithmetic mean of systolic and Diastolic pressure but it comes slightly closer to DBP (because diastole is of longer duration in cardiac cycle)

Extra: - **Mean circulatory filling pressure** – 6 to 7 mmhg.

Pressure exerted by the blood column in the body without being pumped by LV (for ex: stagnation of blood at time of death)

3. **Measurement of BP**

→ Sphygmomanometer – It gives higher pressure readings as compare to directly measured Intravascular pressure – because of dissipation of cuff pressure in the intervening tissue.

Note: - Obesity → Higher pressures come as compare to normal individual due to more dissipation of cuff pressure. Some principle goes for Atherosclerosis

→ Small cuff → High pressure is recorded.

Regulation of BP

Chemical | Neural (short term)

Chemical Regulation of BP

I. Vasoconstrictions

- Vasopressin
- NA
- Angiotensin
- Endothelin – Most potent local vasoconstrictor except when they act via ET_2B then it causes vasodilation
- Urotensin – Most potent circulating vasoconstriction

II. Vasodilators

→ Hypoxia (Except lungs – where it cause vasoconstriction)

→ CO_2/ H^+/ Lactic Acid

Note: - CO_2 locally causes vasodilation but if it accumulates in Medulla as a part of CNS Ischemic Response – then it causes vasoconstriction throughout the body.

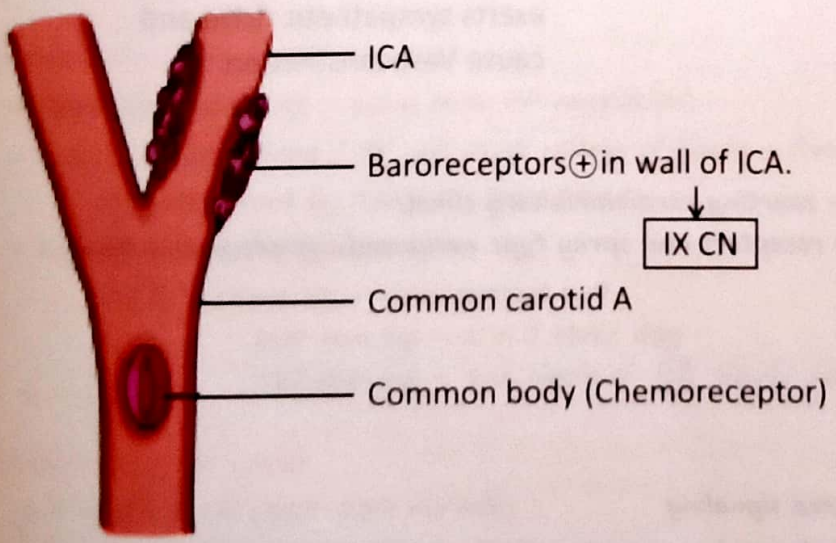
→ **Adenosine** (Especially for coronary circulation) except in kidney it causes vasoconstriction of efferent Arteriole as a part of Tubulo-glomerular feed back

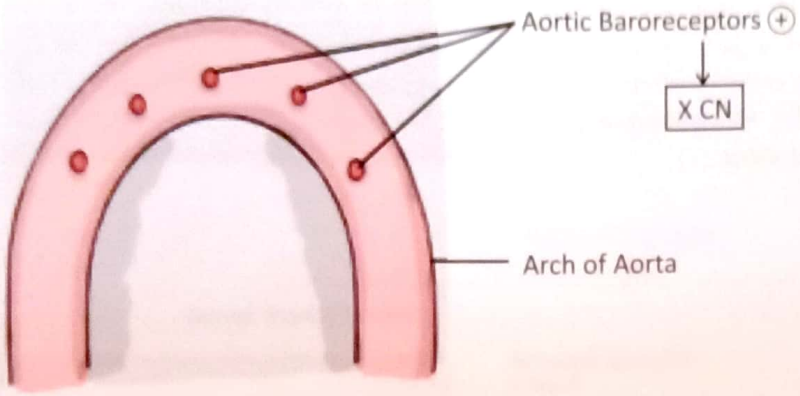
→ Histamine

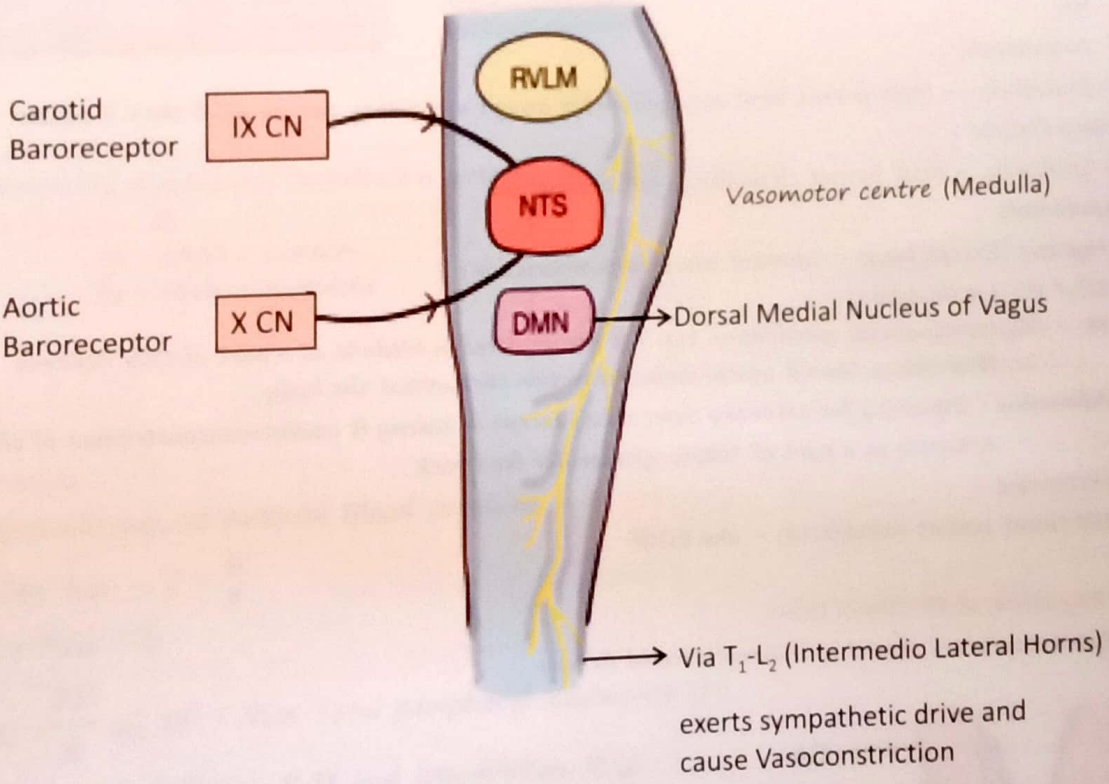
→ NO (most potent vasodilator) – aka EDGF

Neural Regulation of BP (short term)

→ **Baroreceptors**–Located in Internal carotid Artery.







– DMN of vagus – vagal efferent fibers – exerting cardioinhibitory effect.

Baroreceptors are stretch sensitive mechano receptors and spray type nerve endings present in them.

→ They best respond to pulse pressure

→ IX and X nerve are buffer Nerves

Ranges of operation of Baroreceptors

Carotid = 60-180 mmHg

Aortic = 90-210 mmHg

Baroreceptors operate via frequency modulated signaling

→ At 100 mm Hg → Steady Impulse discharge baroreceptors to the vasomotor center

↑ BP - ↑ discharge
↓ BP - ↓ discharge

Note → Highest Impulse Traffic for Baroreceptor is at 180 mmHg and Lowest at 60 mmHg.
→ Baroreceptor system will be most sensitive around 100 m Hg.
→ Cutting of IX and X CN – either of them will cause ↓ in Impulse traffic going to vasomotor center and that is picked up / sensed by vasomotor centre as fall in BP and immediately there is ↑↑ BP within seconds.

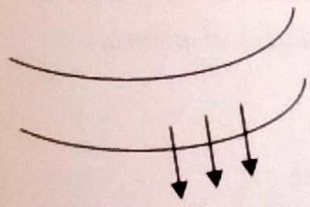
Scenarios

→ BP ↓ 60 – regulated by chemoreceptor mechanism because it was sensed / taken up as Hypoxia and they act via IX and X CN and increase the ventilation and BP.
→ BP ↓↓ <20 mmHg – CNS is chemic Response occurs – aka hast ditch stand
→ ↓↓ cerebral blood flow and therefore CO_2 accumulates near vasomotor centre (Rostro ventrolateral Medulla – RVLM) and intense vasoconstriction throughout body occurs.

Note: - **Cushing Reaction** (variant of CNS Ischemic Response)
↑↑ ICT
↓
ICT > Cerebral Artery pressure
So CNS Ischemia Occurs

Intermediate Regulation of BP → ADH, ANP

Capillary fluid shift mechanism
→ If ↑ circulatory blood volume there will be release of ANP causing Natriuresis and Diuresis
→ Capillary fluid shift mechanism



↑↑ BP causes ↑ in capillary Hydrostatic pressure and it pushes the fluid out of capillaries so there would be decreased circulating blood volume and BP decreases.

Long term Regulation of BP

→ **RAAS** (Intermediate – Long term BP regulation)
- ↓↓ Blood volume / BP will cause release of Renin – formation of AT – I, AT – II and also release of Aldosterone by Adrenal cortex gland.

→ **Kidney – body fluid mechanisms**
- At BP 60mm Hg – Urine output is 0
  100 mm Hg – 1-1.5 litre/ day
  160 mm Hg – 5-6 times of (N) limit/ day

Coronary circulation points

→ 4 to 5% of CO (225-250 ml/min)
→ Autoregulation of Blood flow by Adenosine
→ A – VO_2 difference is highest – 15:20 as comparable to other part of body 5:20 ie. 25%. Heart has

highest O_2 utilization coefficient 75%

→ Blood is reduced mainly in Diastole but there is duality in this statement because

- The Epicardial vessels – The main coronary vessels receive blood during systole.
- The endocardial vessels – they receive the blood during diastole.

→ **Nutrition**: - It primarily uses: -

- Free fatty acids – 67%
- Glucose – 30

Respiratory system

- **Mechanism of Breathing**
- **Gas transport**
- **Regulation of breathing**

Basics

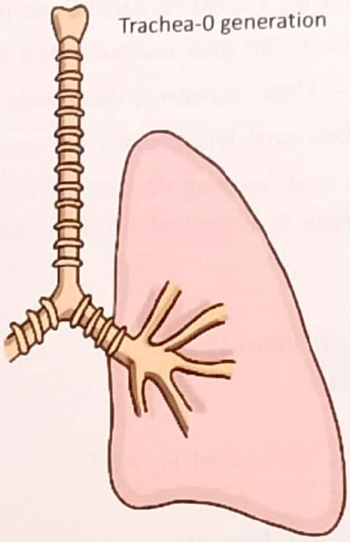
Total of 23 generation of respiratory tree

→ Last 7 generation (respiratory bronchiole, the Atria Alveolar sac) – Respiratory zone

→ Trachea & first 7 generation → have cartilage in their walls

→ Last 16 generation – No cartilage in their walls

so prone dynamic compression and cause obstructive Air disease.



First 16- Conducting Zone

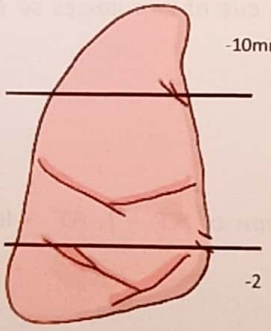
↓

Dead space and no gas exchange occurs

Mechanics of breathing

→ **Intrathoracic / Intrapleural pressure** – Pressure between two layers of pleura – this mostly negative and under most circumstance the negative pressure is because of elastic recoil of lung that is primarily responsible for generating the negative pressure between two layers of pleura.

- Start of Inspiration = -5cm H_2O
  End of Inspiration = -7.5 cm H_2O
- Pressure change of 2.5 cm H_2O during quiet Inspiration is present



At base it is less negative because of weight of lungs and pleura gets compressed and vaccum that results in negativity gets dissipated.

→ **Deep sigh or deep yawn** (forceful Inspiration) - It will produce pressure of -30cm of H_2O

→ First breath/ cry of Neonate after birth produce pressure of -60cm H_2O

→ Maximum –ve pressure is generated in Muller's Maneuver -100cm H_2O

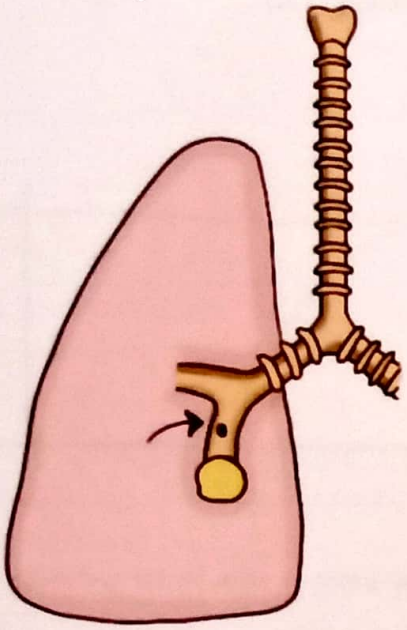
Note: - Positive Intrapleural pressure

→ Strong cough, sneeze = +50cm H_2O

→ Greatest Intrapleural pressure = +100 to 150cm H_2O

2. **Intra alveolar pressure**
   - → At start of inspiration = -1 cm H_2O
   - → At start of expiration = $+1$cm
3. **Transpulmonary pressure**
   - → Pressure across the lung (alveolar-intra pleural pressure)
   - → It is minimum at start of Inspiration it goes on widening during inspiration
4. **Transmural pressure**
   - → Pressure across the airway wall.

(P airway- P interstitium)



Pressure inside the Airway
– Pressure just outside the Airway.
(Interstial pressure)

Alveolar Epithelial cells: (Pneumocytes)

- → Type I – occupies 93% surface area of alveolar and their function is gas exchange.
- → Type II – Occupies 5% surface Area is covered by them their function is to produce surfactant as well as Clara cells.
- → Type III – Occupies 2% surface Area of Alveolus and their function is to work as chemoreceptor cells for the inhaled chemicals.

Note:- Type I and Type II – They exist in ratio of 1:1 in numbers but most of the surface area (93%) is covered by Type I.

Surfactant – produced by Type II Pneumocyte

- → Earliest evidence of surfactant synthesis = 17-20 weeks
- → Surfactant begins to appear = 28-32 weeks
- → Precursor stage for surfactant – Tubular myelin

Constituents in surfactant

- DPPC (Di palmitoyl phosphatidyl choline)
- Surface Apoprotein
- Ca^{++} (required for faster spread of surfactant)

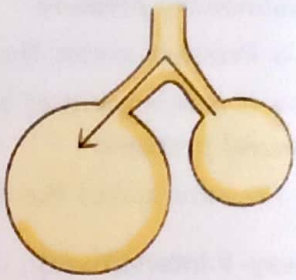
Functions of surfactant:

- → ↓↓ surface tension (↓ collapsibility of during)

→ ↑ lung compliance (↑ distensibility of lung)

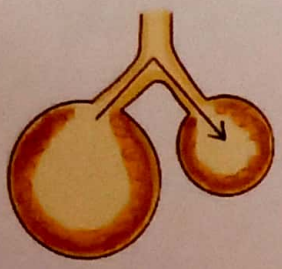
→ Keep alveoli dry and stabilizes the alveolar system of Interdependence.

Note:- **Alveoli follows Laplace's law** = $P = \frac{2T}{R}$



→ So in absence of surfactant ↑↑ P (pressure) more in smaller Alveoli because 'R' is less and air goes from small alveoli to large Alveoli

→ But in presence of surfactant the surface tension is ↓ dramatically (T↓↓)



Compliance

→ Measure of distensibility

→ Compliance = $\frac{\Delta V}{\Delta P}$

→ Compliance x $\frac{1}{ST\ (surface\ tension)}$

3 types of compliance seen:

→ **Static compliance** (when lungs are stationary)
= 200ml/ cm H_2O for every 1 cm of H_2O, change around lungs the distention of lungs changes 200 ml.

Note: During Inspiration the intrathoracic pressure change is -2.5 cm H_2O so the total distension of lungs = 200 x2.5 = 500 ml

→ **Specific compliance** = $\frac{Compliance}{FRC}$

→ **Dynamic Compliance** - Changing ΔV /ΔP

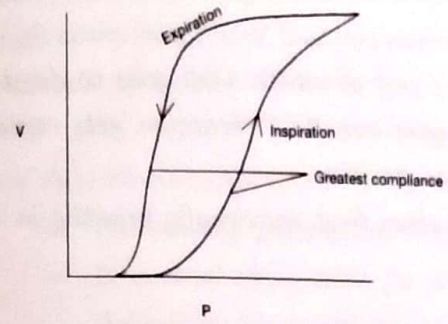
Note: - At lower lung volumes compliance is high because at low lung volume –small alveoli so surfactant is concentrated in that area and surface tension ↓↓ dramatically. (At start of Inspiration or end of expiration).

→ At higher lung volumes – surface tension ↑ and compliance is low.

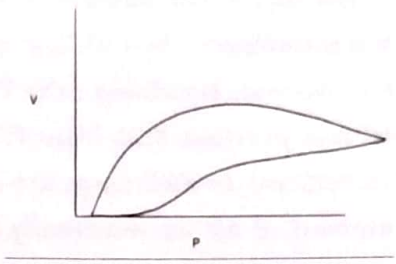
- In Restrictive lung disease: - The best way to breathe – shallow and rapid near lower volumes
- In COPD – slow and deep near the higher Lung volumes.

Hysteresis:-Pressure-Volume relationship

Dynamic compliance

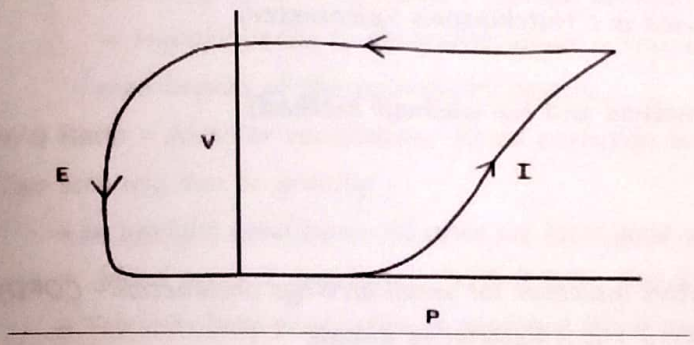


In Restrictive diseases



→ Pressure is increasing but volume is not going up

COPD



→ Expiration covering lot of area – More work done during expiration.

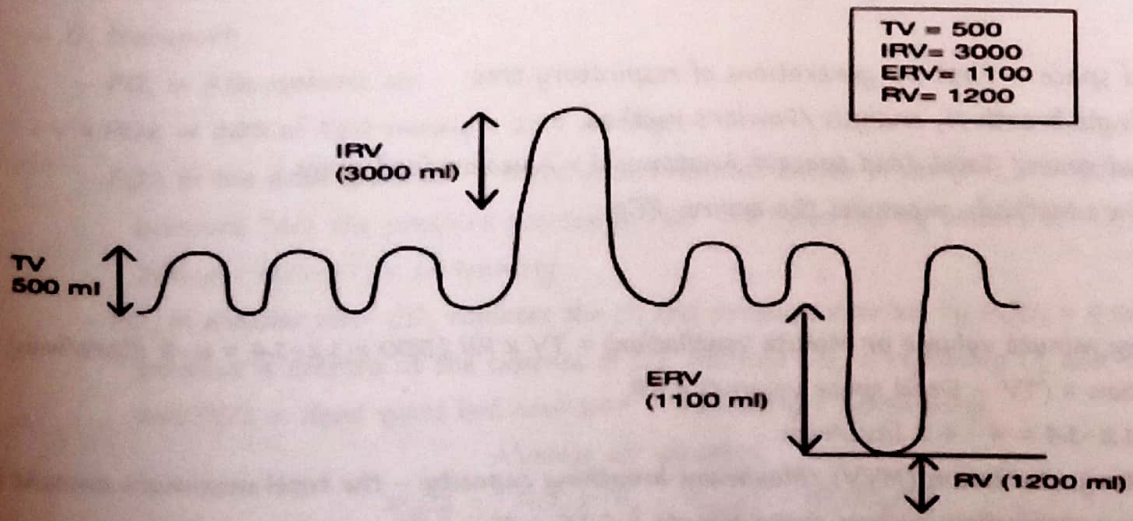
Work of breathing in normal individual

→ Compliance work (65%)

→ Airway Resistance (25%) (↑↑ in COPD)

→ Tissue Resistance work (7%) (↑↑ in /LD)

Lung volume and capacities



→ **Inspiratory capacity** (total volume of air that we can inspire)
= TV (500ml) + IRV(3000ml) = 3500ml

→ **FRC** (Functional Residual capacity) – The amount of air that remains in the lungs at the end of quiet expiration. = ERV + RV = 2300ml

Note:- In case of fresh cycle of Normal breathing 500 TV comes in – out of which 150 goes to dead space out 350 ml goes into FRC and previous 350 from FRC (230ml) goes out. 1/7th fraction gets replaced with each breath = 350/2300 ml .In FRC lungs are at equilibrium position.

→ **Vital capacity** – The amount of air we maximally breathe out after first maximally breathe in = IRV + TV + ERV.

→ **Total lung capacity**= IRV + TV + ERV + RV

Extra:- **Closing lung volume** – just above residual volume starting from peak of TLC
= IRV + TV + ERV – the airways near the base of lungs begins to close.

Spirometry (Spirogram (graph) is made and instrument used is – Hutchinson's Spirometer)
Volume cannot be measured by spirometry:-
→ Residual volume (measured by the Helium dilution method and N2 washout method)

FEV$_t$ (Timed vital capacity/ Forced vital capacity)
→ FEV$_1$ = 80-83%
- (FEV$_1$ < 70% indicates obstruction/and it is the sensitive indicator for small airways obstruction- COPD)
- FEV$_1$/VC ratio = if < it is COPD (obstructive diseases), if > it is Restrictive disease
→ FEV$_2$ = 90-93%
→ FEV$_3$ = 97%

Note: when we exhale the air out – Firstly the air is coming from large airways, the middle part of air is coming from small airways and last air is coming from alveoli. FEV1 is divided into 4 equal parts and the middle two parts are taken FEV$_1$ 0.25- 0.75 called as "Maximum mid expiratory flow rate" ,the normal value is 3-3.25 litre/sec, if it is decreased it is the most sensitive indicator of small airways obstruction.

Dead Space
→ Normal value – 1ml/pound of body weight. (Normal adult 150 pound so normal value is 150ml)
→ Two types:-
- Anatomical dead space – First 16 generations of respiratory tree
  - Measured by "Single breath N_2 analysis /Fowler's method
- Physiological dead space/ Total dead space = Anatomical + Alveolar dead space
  - Measured by Bohr's Method- measures the expires PCo_2

Indices:-
→ **RMV (Respiratory minute volume or Minute ventilation)** = TV x RR (500 x 12-14 = 6-8 liters/min)
→ **Alveolar ventilation** = (TV – Dead space volume) x RR
- (500-150) x 12-14 = 4- 4.2 litre/min
→ **Maximum voluntary ventilation (MVV) /Maximum breathing capacity** – the total maximum amount of air that ventilate our respiratory system every minute = 125-170 L/min.
→ **Breathing reserve** = MVV – RMV
→ **Dyspneic Index** = (**BR/MVV x 100**) Point where the breathlessness occurs. Normal value is 95% and

when it falls below <70% Dyspnea occurs – Dyspnea point

Pulmonary circulation

→ It is called Lesser circulation; lungs have 15-18% of blood volume at any given time.

→ High compliance and low resistance circulation, due to high compliance the lungs are called the reservoir of blood.

Lungs have dual blood supply:-

→ Pulmonary circulation – Gas exchange

→ Bronchial circulation (1-2% of total blood volume) – O_2 supply to connective tissue of lungs. Bronchial venous blood goes into pulmonary vein (O_2 Blood) and it comes to left side of heart.

Note:

→ Left side of heart receives 1-2% extra blood compare to right side because bronchial venous blood is mixing in left side blood – Venous admixture of blood in the left side of heart.

→ Hypoxia leads to vasoconstriction – because of O2 sensitive K+ channels in the smooth muscle cell membranes of the pulmonary vessels.

V/Q Ratio = Alveolar ventilation/ Blood perfusion to alveoli = $\frac{4\ L/min}{5\ L/min} = 0.8$

Two scenario due to gravity:-

→ In upright condition- At apex we have good ventilation but less perfusion (because heart pumping blood against gravity) so, V/Q is 3.5 , this is called as physiological dead space.

→ Towards base ventilation is good but blood perfusion is much higher, V/Q is 0.5 , known as physiological shunt.

Diffusion capacity of Respiratory Membrane:- DLCO

→ CO is used to measure the DLCO = 21-23 ml/min/mmHg (For 1mmHg of pressure gradient across the membrane in 1min, 21-23 ml of gas will diffuse through respiratory membrane), CO is used because it never reaches equilibrium from alveolus to pulmonary capillary blood – Diffusion limited gases.

→ O_2 and CO_2 cannot be used to measure DLCO because it reaches equilibrium very rapidly from alveolus to blood – Perfusion limited gases

Gas transportation:-

→ **O_2 transport**

- **PO_2 in Atmospheric air**
- PO2 → 20% of 760 mmHg = 159 mmHg
- **PO2 in the dead space air** – there occurs humidification of air (PH_2O = 47mmHg), so out of total pressure 760, the pressure exerted is 760 – 47(exerted by water) so PO_2 in dead space air = 20% of (760-47) = 149mmHg
- **PO_2 in alveolar air:-** CO_2 replaces the O_2 and pressure exerted by PCO_2 = 45mmHg and this pressure is exerted at the expense of O2 ,because CO_2 is replacing O_2 and therefore 149mmHg was PO2 in dead space but now 149 – 45mmHg = 104mmHg

Alveolar air equation

$$P_AO2 = [\ FIO_2 \times (P_B - P_{H2O})\ ] - [P_ACO_2/R]$$
$$= [\ 20\% \times (\ 760 - 47\ )\ ] - [\ 45/R\ ]$$

- **R = Respiratory Quotient** = CO_2 evolved/O_2 consumed ;

- Normal value is 0.8
- Carbohydrate rich diet value is 1.0
- Fat rich diet 0.7
- **PO_2 in the arterial blood** – Alveolar PO_2 is 104, and immediately within 0.3 sec, O_2 reaches equilibrium from alveolus to blood, therefore PO_2 in the pulmonary capillary blood will be 104 and this blood will go to the left side of the heart and due to venous admixture of blood (bronchial venous blood), the PO_2 will further decrease and become 95mmHg and this blood is pumped into artery – So PO_2 in arterial blood is 95 mmHg.

$AaDO_2$ = Alveolar PO_2 – Arterial PO_2
= 104-95 = 9-11 mmHg

This is influenced by certain conditions:-

	Alveolar PO_2	Arterial PO_2	$AaDO_2$
Right to left shunt	Normal	Decreased	Increased
ILD	Normal	Decreased	Increased
Hypoventilation	Decreased	Decreased	Increased

O2 transport in blood:-

→ Hb – 97%

→ Free/dissolved in plasma – 3%, free O_2 exerts the partial pressure in , free O2 which exerts the partial pressure of O_2

Free or dissolved O2 content = PO_2 x Solubility coefficient (0.003ml/100ml/mmHg).

O_2 carried by Hb (O_2 carrying capacity of blood)

→ 1 gm of Hb – if 100% saturated; it carries 1.39 ml of O_2

→ Hb does not getting 100% saturated; the maximum saturation of Hb is up to 97% so 1gm of Hb carries 1.34ml of O_2. (Person Hb is 15 gm% so total O2 carrying capacity is 15x1.34 = 20.1 ml of O_2)

Total O_2 content = O_2 carried by Hb + O_2 carried in plasma

=[Hb(gm%) x 1.39 x %sat] + [PO_2 x solubility coefficient for O_2]

→ Under normal circumstances 19.6ml by Hb (97%), 0.4ml by plasma (3%) = 20ml of O_2 is carried by every 100 ml of arterial blood.

Note:- The aim of hyperbaric O_2 chamber in CO poisoning – to increase the dissolved O2 content in plasma. As in case of CO poisoning Hb becomes useless, so aim is to improve O2 content by plasma- from 0.4ml up to 6ml/100 ml of blood, because 6ml O_2/100ml of blood is the minimal amount needed for survival.

O_2 utilization coefficient

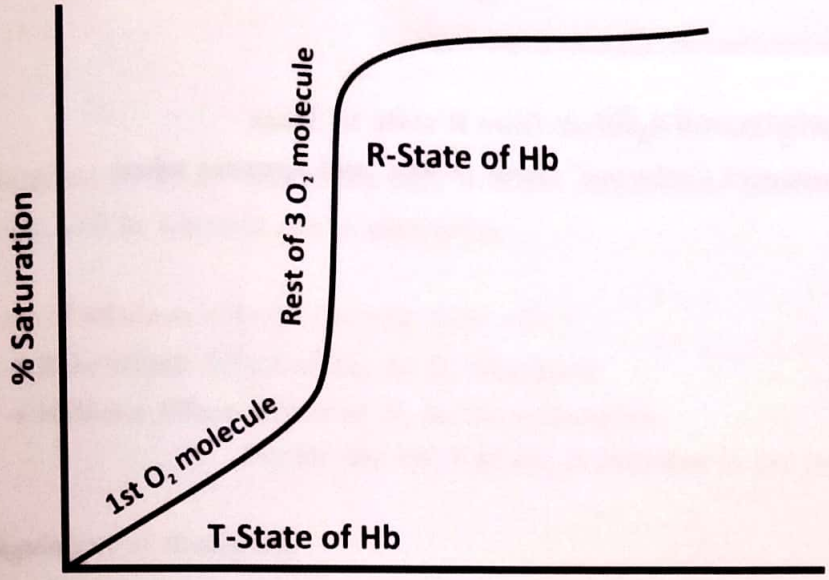
20ml of O_2 is carried by every 100ml of arterial blood, when it comes to the tissue out of this 5ml is extracted by tissue under resting metabolism(A-V difference), 5/20= 25% is the O_2 utilization by most of the tissues.

Ex:- Calculation of O_2 consumption by body; if the cardiac output is 5 liters:- 5ml is extracted by tissues and utilized from every 100ml of blood coming, so if total blood is 5 liters then O2 extracted is 250ml.

Note:-

A-V O_2 difference is 25% for most of tissue, but **highest in Heart (coronary circulation)= 75%**:- that means in coronary circulation 15ml of O_2 is extracted out of 2ml O_2 being carried per 100ml, **least in kidney = 10-12%** :- because kidney is small organ with massive blood supply.

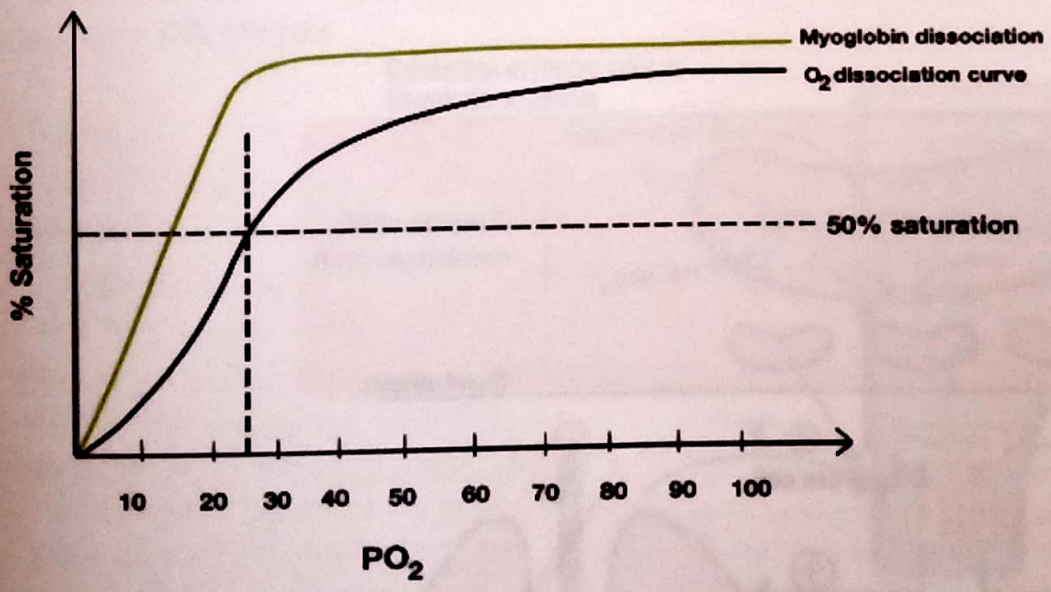
O_2 dissociation curve - S-shape and sigmoid shaped



→ % Saturation rises slowly initially then rises steeply

→ Every Hb molecule carries 4-O_2 molecules. 1st out of 4- O_2 molecules that starts combining to Hb occurs slowly because in deoxy Hb-globin chains are in T-state and in this T-state the O_2 affinity is low - So first O_2 molecules combine slowly with Hb molecules.

→ After T state, the Hb molecules goes into R- state Affinity is Higher and there is positive cooperativity among O_2 molecules. Therefore 2nd, 3rd and 4th molecule of O_2 combine rapidly and that is indicated by the steep rise in Curve.



→ P_{50} for Hb = PO_2 at which Hb is 50% saturated.

→ P_{50} for Hb = 25-28mm Hg.

→ P_{50} for Myoglobin = 5 mm Hg → Myoglobin dissociation curve is rectangular Hyperbola.

Shift to Right → (Hb liberates O_2 more readily even in range of 100 to 60 mm Hg of Po_2)

- ↑↑H^+
- ↑ PCO2 ⟶ BOHR's effect } Occurs in Tissue
- ↑ Temp
- ↑ 2,3 - DPG ⟶ Occurs in RBC

→ First three shift the curve to Right by flipping the Hb molecule from R state to State.
→ Last ↑ 2,3 – BPG in RBC occurs in the "Rappaport Luebering" shunt in RBC and happens when acclimatization to high altitude is needed.

Shift to Left

→ Hb does not liberate O_2 readily, it occurs in

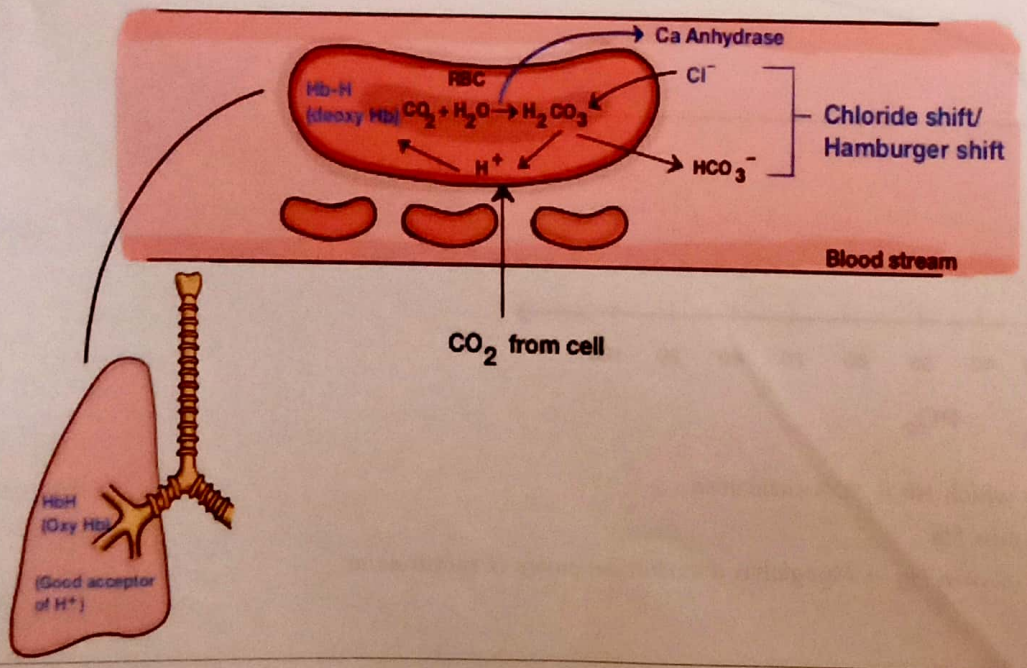
- ↓↓ H^+
- ↓ PCO_2
- ↓ Temp
- ↓ 2-3-DPG
- CO poisoning
- HBF

In case of CO poisoning – binding of CO with Hb increases the O_2. Affinity for remaining binding sites on Hb.

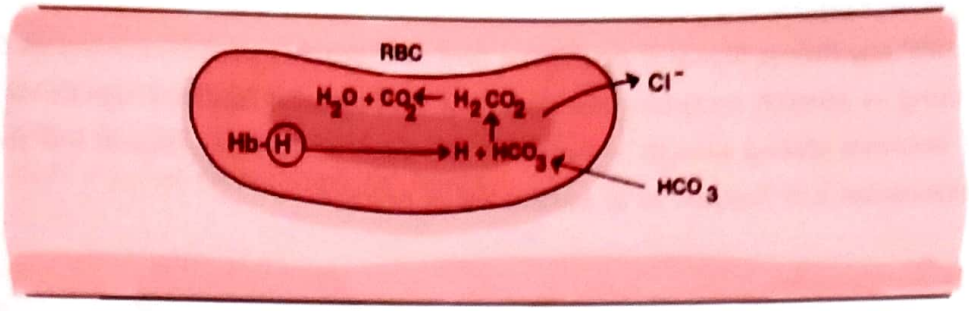
CO_2 transport

→ 70 % transport occurs in form of $HCO3^-$
→ 20-25 % in form of Carbamino Compounds
→ 5-7 % as free (dissolved in plasma)

Co_2 transport:-



In lungs: Reverse happens



CO_2 will be expelled out in Expiration.

Inspired O_2 which enters the RBC in blood stream and combine with Hb and displace the H^+ from Hb.
→ Co_2 will be expelled out in expiration.

Basis of Haldane effects/ Reverse Bohr effect

→ **Bohr effect**: Effect of Co_2 on O_2 transport

→ **Haldane Effect**: Effect of O_2 on Co_2 is liberation

Double the Vol % of Co_2 is liberated in the presence of O_2

Regulation of Breathing

→ Neural

→ Chemical

Neural

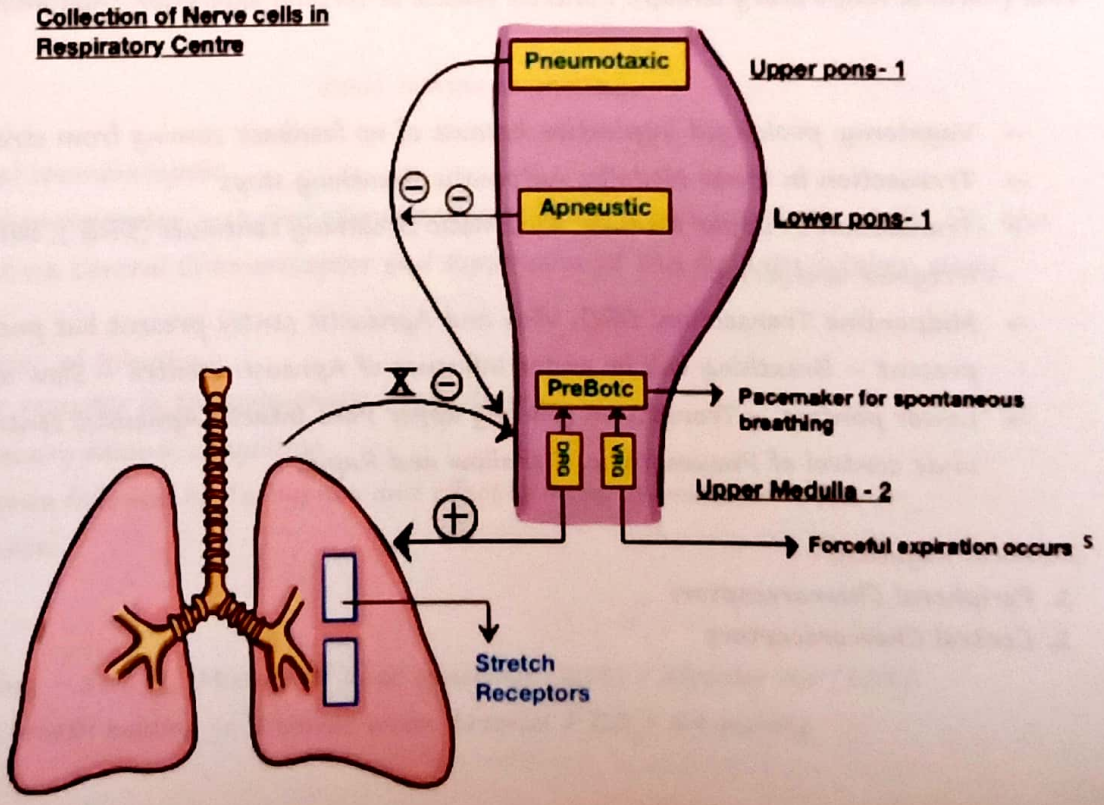
→ Voluntary (Cortex)

→ Automatic (Brain Stem)

Note:- Ondine's Curse - Automatic regulation stops and person depends on voluntary breathing.
It is seen with:

- Bulbar Poliomyelitis
- CO_2 Narcosis

Collection of Nerve cells in Respiratory Centre



DRG – Dorsal Respiratory group

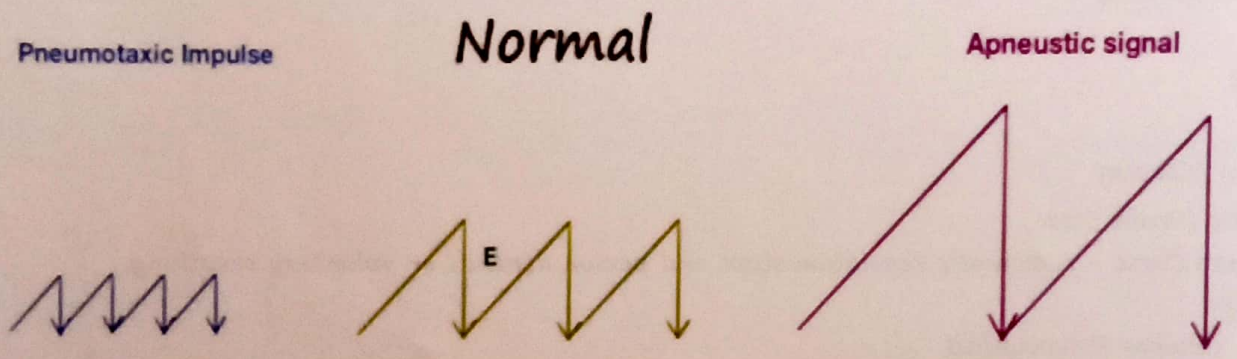
→ Inspiratory Ramp Signal is generated and as it reaches peak/ increases in Strength – Thoracic cage is distending → stretch receptors are distorted – They send feedback signals via and when the feedback signal becomes strong enough – Suddenly the Inspiratory Ramp Signal will stop abruptly. Inspiration stops and expiration will happen as of passive recoil process.

Pre Botzinger Complex

Pace of Automatic Breathing is controlled by a nearby centre in upper medulla.
Note: Inspiratory Ramp signal is generated in DRG but pace is controlled by Pre Botzinger complex because Neurons of DRG and VRG – They form synapses with pre Botc.

Apneustic and Pneumotaxic Centre: Together they control the rate and depth of breathing
→ P. centre: Causes early switch off of the Inspiratory Ramp sing.
→ A. centre: Does not allow the early switch off by D. centre.

Note:
Apneustic Breathing: There is prolonged Inspiration and at end of that there is spasm in Inspiration



VRG (Ventral Respiratory Group): Controls muscle of forceful expiration (Abdominal Muscles)

Lesions at various levels

- → **Vagotomy:** prolonged Inspiration because of no feedback coming from stretch receptors.
- → **Transection in lower Medulla:** Automatic Breathing stops
- → **Transection in upper Medulla:** Automatic Breathing continues (DRG), but berthing is slightly Irregular and jerky.
- → **Midpontine Transection:** DRG, VRG and Apneustic centre present but pneumotaxic centre is not present – Breathing will be under Influence of Apneustic centre – Slow and deep.
- → **Lower pontine – Transection (Slaving upper Pons Intact):** Apneustic centre is affected – breathing unde control of Pneumotaxic. C shallow and Rapid.

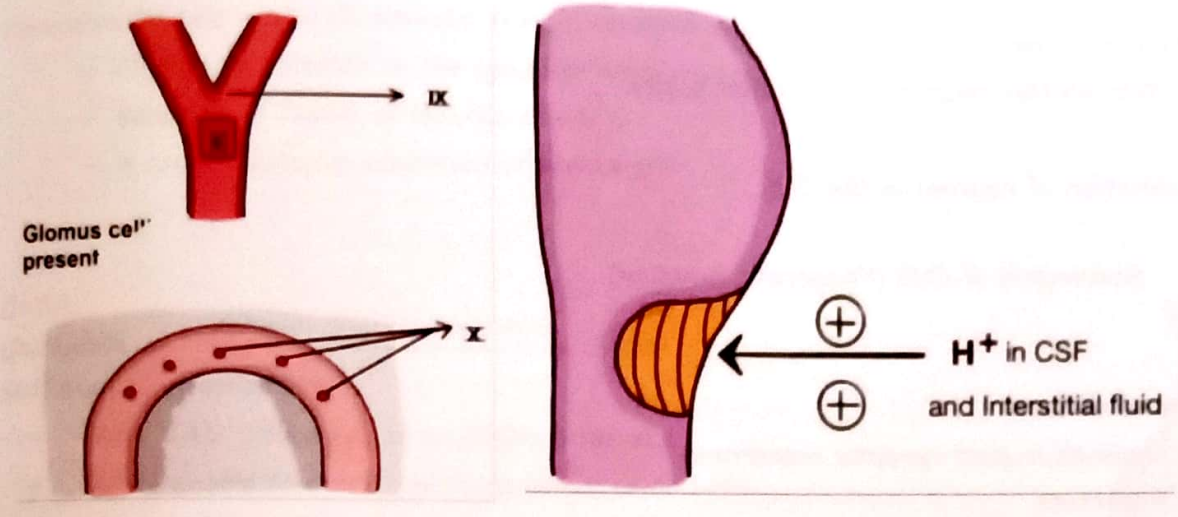
Chemical Regulation

1. Peripheral Chemoreceptors
2. Central Chemoreceptors

Peripheral Chemoreceptors

→ They are sensitive to Arterial H^+ (Metabolic Acids), Hypoxia.

Note: Hypoxia stimulates peripheral chemoreceptors and then that will send signals via IX and X Nerve to respiratory centre. Hypoxia does not drive the ventilation until PO_2 has fallen below 60 mmHg (Normal 100 mmHg).



Central Chemoreceptors

→ Present in Ventral Aspect of Medulla – 150 mm beneath

→ They respond to changes in Arterial CO_2.

→ ↑ Co_2/ H^+ - Stimulates central chemoreceptors

→ ↓ Co_2/H^+ - Depresses Central Chemoreceptors

If there is hypoxia peripheral chemoreceptors will be stimulated and ventilation is stimulated → Co_2 + H^+ washout and Ventilation is again depressed. So effect of Hypoxia is not seen. Only When Po_2 falls < 60 there occurs Hypoxic stimulation of peripheral chemoreceptors that is so strong that it will override the effects of Co_2 washout on Central Chemoreceptors – then Hypoxia will continue to drive the breathing.

Acclimatization

→ ↑ 2, 3 DPG

→ ↑ Sensitivity of peripheral chemoreceptor

→ ↓ Sensitivity of central chemoreceptor – so that stimulated ventilation is going to washout the Co_2 and H^+ and that is going to act via Central Chemoreceptor and suppression of this Activity is taken away.

Quick points regarding regulation of Breathing

J-receptors: Juxta Alveolar receptor in the pulmonary interstitium.

→ It is stimulated by pulmonary edema, congestion

→ It acts in the form of Apnea followed by Tachypnea and effect of vagal stimulation is seen – Bradycardia and Hypotension.

Extra

→ Mouth to Mouth Breathing – 16% O_2 (Mixture of dead space Air (20%) + Alveolar Air (10%))

→ Breakpoint in voluntary breath holding → It comes when Arterial P CO_2 > 49 mmHg

CNS

Two types of cells in CNS

1. Neurons
2. Glia

a) **Macroglia**

→Astrocytes

- reinforce the blood brain barrier
- involved in neurotransmitter reuptake and redistribution

→oligodendrocyte

- involved in myelination of neurons in the CNS
-

b) **Microglia** → Scavengers of CNS (Phagocytic function)

Neurotransmitter

1. **Excitatory Neurotransmitter**
   - → Open Na^+/ Ca^+ channels in post synaptic membrane
   - → Eg Glutamate, Aspartate
2. **Inhibitory Neurotransmitter**
   - → Open K+/Cl- channels in post synaptic membrane, hyperpolarize it
   - → Eg GABA (in Brain), Glycine (Spinal cord)

Low Molecular Weight NTS	High Molecular Weight NTS
→ Ach → Noradrenaline → Glutamate	→ Opioids → Neuropeptide Y → CART (Satiety) → 2- AG, Anandamide.
→ Synthesized locally	→ Synthesized in Nerve cell body

- → Cerebellum - Highest Neuron population
- → Serotonergic Neuron → found in Nucleus Raphe magnus
- → Noradrenergic Neurons → found in Locus Coeruleus
- → Dopaminergic Neurons → found in Substantia Nigra, Nucleus Accumbens (D3) (area involved in reward and addictive behaviour)

Glutamate – Commonest excitatory receptor In the brain

3 types of Receptor

1. Kainate
2. AMPA
3. NMDA – 3 cations, 2 ligands- voltage gated ion channels.(basis for long term memory)

Mechanism of action of glutamate

- Glutamate released from pre synaptic membrane
- Combines with receptor portion
- Partial depolarization of membrane takes place

- This removes the Mg++ block on cationic channel completely opening it
- Full depolarization occurs
- Some glycine binding is necessary for this action to work

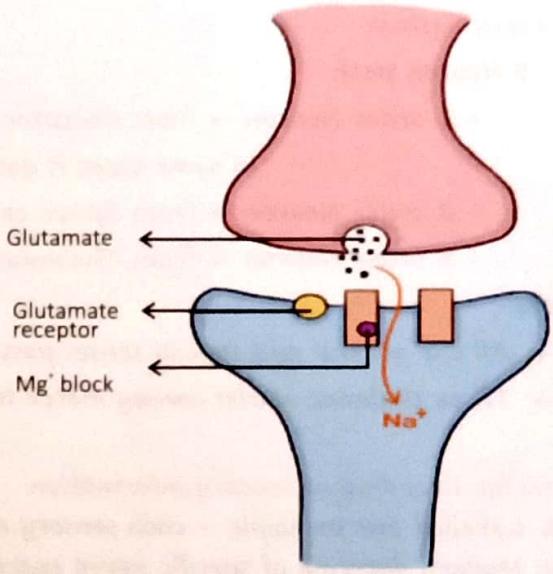
Usually glutamate act as inhibitory neurotransmitter but in brain it act as a facilitatory neurotransmitter as it facilitates glutamate action on the receptor

Penumbra Disease - a/w Glutamate; seen in cerebral ischemia
- Glutamate released In the synapses is not cleared
- Beacause of failure of Na+/K+ Pump
- It causes excessive excitation of membrane

GABA

Glutamate $\xrightarrow{\text{glutamate decarboxylase (GAD)}}$ GABA

Stiff man syndrome (SMS)
→ Anti GAD is formed, so no GABA is formed
→ UMN unable to exert inhibitory influence on LMN
→ Excess glutamate lead to hypertonia



Synapses

1. **Electrical** (very few in the human)
→ Retina
→ Inferior olive
→ Heart

2. **Chemical**

1. Axodendritic (>95%)(m/c)
- these are excitatory

2. Axosomatic (2-3%)
- these are inhibitory
- E.g. 1. Basket cells on Purkinjee cell
2. Renshaw cell in anterior Motor Neuron

3. Axo-Axonal Synapse → involved in presynaptic inhibition of pain afferents.
4. Dendro-dendritic Synapses

Property of Synapses
1. One way conduction
2. Delay at every synapse (0.5 m sec).
3. Fatigue on repeated stimulation
4. Post – tetanic potentiation
5. Inhibition

Synaptic potentials

1. EPSPs – Excitatory Postsynaptic Potential
   - Summation of EPSP required to generate an action potential
   - Two types of summation - Spatial and Temporal
   - Time frame for summation – 15 ms

EPSP	AP
Localised change	Propagated change
Decremental	Non-decremental
Graded response	All or none
Monophasic change	Biphasic change

2. IPSPs – Inhibitory Post Synaptic Potential

Sensory System

→ 3 Neuron path
- 1 order Neuron → from Receptor to spinal cord
  - In some cases it goes all the way to upper medulla like fine touch sensation
- 2 order Neuron → from Spinal cord to thalamus
- 3 order Neuron → from Thalamus to sensory cortex

Note:

→ All the general and special senses pass through thalamus except sense of olfaction.

→ Three thalamic Nuclei convey Motor function → Ventro-anterior, ventrolateral, centromedian.

Law for Encoding of sensory information

1. Labelled line principle – each sensory modality Is carried by a specific tract
2. Muller's doctrine of specific nerve energies
3. Law of projection e.g. → Phantom limb
4. Intensity discrimination

Scale of AP frequency change is given by 2 laws

→ **Weber Fechner law**

$S = K \times \log (I)$

→ **Steven's Power law**

$S = k \times (I)^n$

- S = sensations felt by the cortex
- I = intensity applied

Bell Magendie Law - anterior spinal nerve roots contain only motor fibers and posterior roots only sensory fibers

Receptor physiology

→ Receptor are biological transducers, they convert any form of energy into electrical impulse

→ Normally the transmitter and spike generation occurs at different locations but in case of olfactory neuron it occurs on same cell

→ In case of sensory neuron at skin First AP is generated at the 1st Node of Ranvier but for all other neurons, first AP is generated at Axon hillock

→ Receptor potential = 10 mv – 100 mv

→ More the intensity more the amplitude

→ Receptor potential is a depolarizing potential Except – Rods (hyperpolarizing potential)

Classification of Receptors

1. **Mechanoreceptors**
   - → Merkel disc
   - → Meissner
   - → Pacinian
   - → Ruffini's
2. **Thermo Receptor**
   - → TRP super family receptors e.g. → CMR (cold and menthol sensitive receptors)
3. **Chemoreceptor**
   - → Taste Receptor
   - → Smell Receptor
   - → Globus cell in carotid body
4. **Electromagnetic Receptor**
   - → Rods and cones
5. **Nociceptors**
   - → Also belong to TRP super family
   - → TRP – V (Vanilloid)
   - → TRP – A1 (Ankyrin)

Adaptation

1. Rapidly adapting receptor/ phasic receptors
   E.g. → Pacinian Corpuscle
2. Slowly adapting/ Non-adapting/ Tonic receptor
   E.g. → pain Receptor

Temperature Receptor

→ a/k/a Tonic – phasic receptor

→ Tonic – cold receptor → 10 – 30 (22-24 C)

→ 32 - 42 C → Warm Receptor

→ Beyond 45 C cold receptor activate – k/as paradoxical cold.

Receptor	Location	Receptive field	Speed of adaptation	Sensation encoded
1. Merkel disc	Epidermis	Smallest	Slowly	Location of touch
2. Meissner	Dermis	Small	Rapidly	Speed of application of touch Reading of braille
3. Pacinian	Dermis and Deeper structure	Large	Very rapidly	Vibration
4. Ruffini's	Tendon, ligament, joints	Large	Slowly	Deep pressure

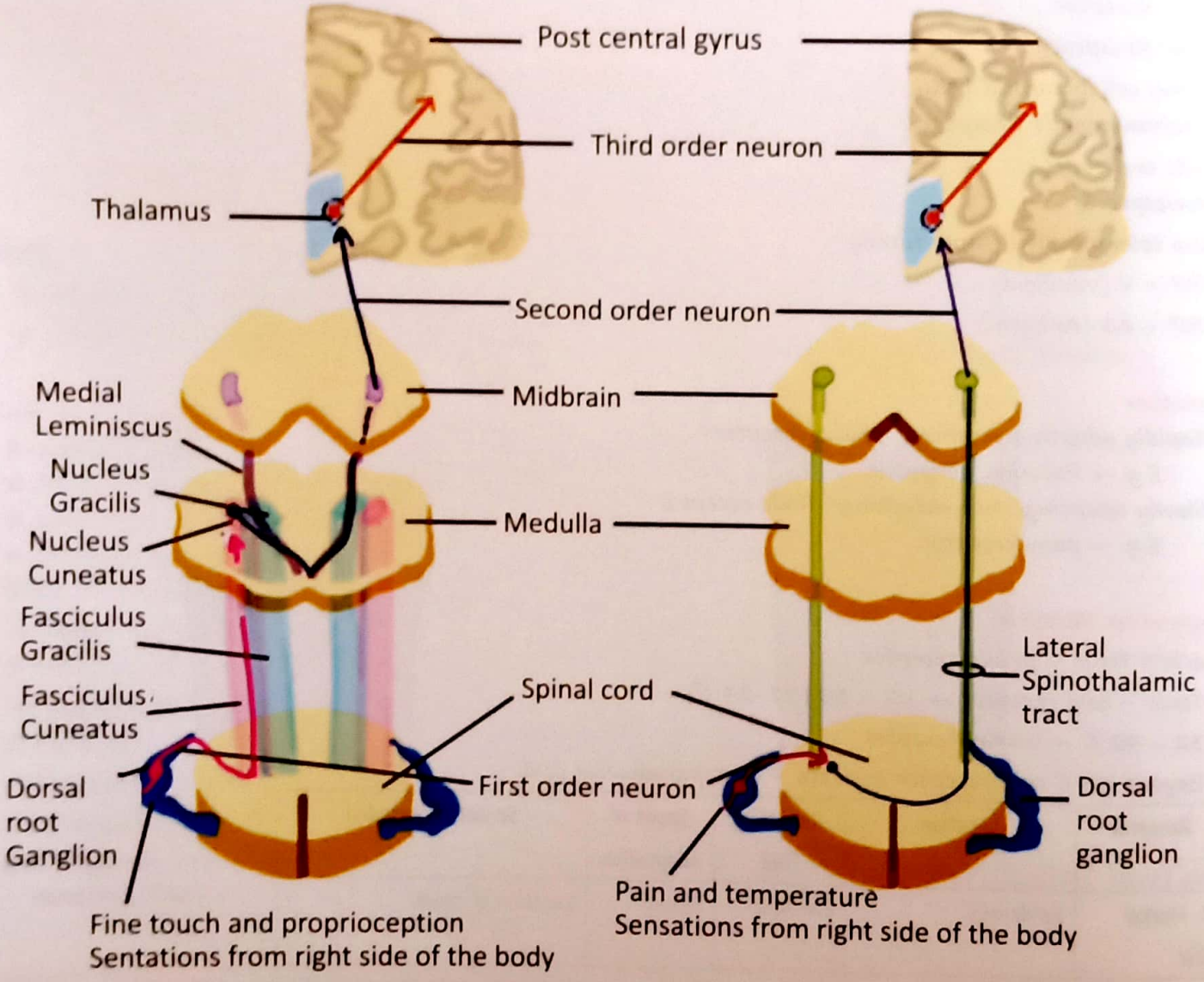
Ascending Tracts

1. Dorsal column System: Fine touch (two point discrimination), pressure, vibration, proprioception (conscious).

Note: unconscious proprioception carried by spinocerebellar tracts

2. Anterolateral system: Crude touch, pain, temperature, tickle, itch, sexual sensation.

Dorsal Column	Anterolateral
→ Epicritic Sensation (need intact cortex)	→ Protopathic sensation (can be felt at the level of thalamus)
→ A α, Aβ fibres	→ A δ, C type fibres
→ Velocity is 70-120 m/sec	→ Velocity is 5-30 m/sec



Dorsal column system

Spinothalamic tract

DORSAL COLUMN

Fine touch from upper limb

→ 1°Neuron enters the spinal cord and divides into 2 branches
- One branch comes anteriorly and synapses in the anterior horn cell – serves as Reflex arc
- Other branch turns backwards and runs upward in dorsal white column

Fine touch from lower limb

→ 1°Neuron enters the spinal cord and start running upwards through lumbosacral segments
- In the cervical region, upper limb fibers push the lower limb fibre to the midline, creating 2 distinct ascending tractsin white column:-
  - Fasciculus gracilis → Bundle near the midline coming from LL
  - Fasciculus Cuneatus → Bundle placed laterally, coming from UL.

Note:- Stereo genesis is lost in the lesion of Fasciculus cuneatus.

→ Fasciculus gracilis/cuneatus – tract of Goll and Burdach (old name)

→ 1°Neuron ends in upper medulla, in nucleus gracilis and nucleus cuneatus.

2° Neuron:- starts in upper medulla and crosses midline and runs in medial lemniscus and joined by trigeminal nerve and ends in thalamus.
- 2° Neuron of dorsal column end in ventrolateral nucleus.
- Trigeminal nerve ends in ventromedial nucleus of thalamus

ANTEROLATRAL COLUMN

Pain from upper limb

→ 1°Neuron enters the spinal cord and ends there

→ 2° Neuron starts from dorsal horn and crossed midline in anterior commissure and ascends up as Lateral Spinothalamic tract to thalamus.

Pain from lower limb

→ 1°Neuron enter spinal cord and ends there.

→ 2° Neuron starts and crosses midline and runs upwards in lateral white column

→ UL fibre joins lower limb fibre and LL fibre pushed laterally.

Arrangement of fibers in lateral white column (from lateral to medial)

LL → abdomen → UL , so in the tumor of lateral column, 1st sensation affected is – pain from opposite side of LL.

Sensory System

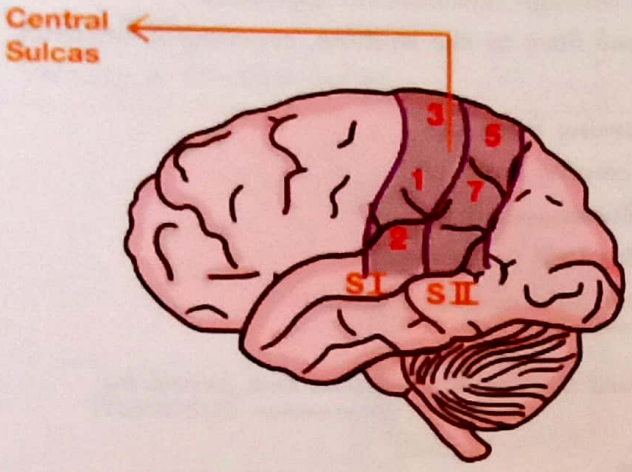
Area: 3, 1, 2 → S I → Perception of touch sensation.

Area: 5, 7 → S II → Analysis and Interpretation.

→ Body presentation is → contralateral
→ Inverted
→ Vertical orientation

→ Largest representation is of lips and face in sensory cortex

→ In motor cortex largest representation is of muscles of speech and thumb.



Physiology of Pain

Pain insensitive structure

→ Brain substance
→ Lung Parenchyma
→ Liver parenchyma
→ Kidney
→ Intestine (Sensitive only to torsion pain)

2 Types of pain

→ Fast/ Sharp/ Acute pain → Carried by Aδ → Neospinothalamic tract. Neurotransmitter released is glutamate

→ Slow/ chronic pain → C type fibres → paleospinothalamic tract.
Neurotransmitter released is substance P

Varieties of pain

1. **Physiologic:** Starts from the receptor
a. Allodynia: non noxious stimulus
b. Nociceptive pain: noxious stimulus
c. Hyperalgesia : noxious stimulus produces exaggerated pain & is usually Inflammatory.
Two types : Primary – when noxious stimulus applied at the site of pain
Secondary – when noxious stimulus applied away from the site of pain

2.Pathological: It is a neuropathic pain i.e. triggered by the nerve.
- Causalgia: electric shock like pain/ burning pain after crush injuries
- Post herpetic neuralgia

- Thalamic pain
- Phantom pain

Analgesia system:

1. Gate Control theory of pain: Lamina 2 and Lamina 3 is substantia gelatinosa & is the gate for pain transmission.
Accu-pressure is based on gate theory, once the pressure carrying fiber is stimulated causes inhibition of the pain carrying fiber.
2. Descending Analgesia system: Component of descending analgesia system →

Periaqueductal grey
↓ projects enkephalinergic neurons
Nucleus Raphe magnus
↓ projects serotonergic neurons
Pain inhibitory complex on dorsal horn (Neurotransmitter is enkephalin)

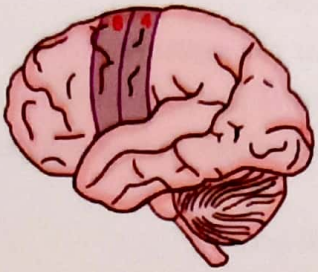
3. Opioids: All the three opioids to all the three receptors but there is preferential binding of Endorphins with μ receptor, Enkephalins with δ receptor & Dynorphins with κ receptor.

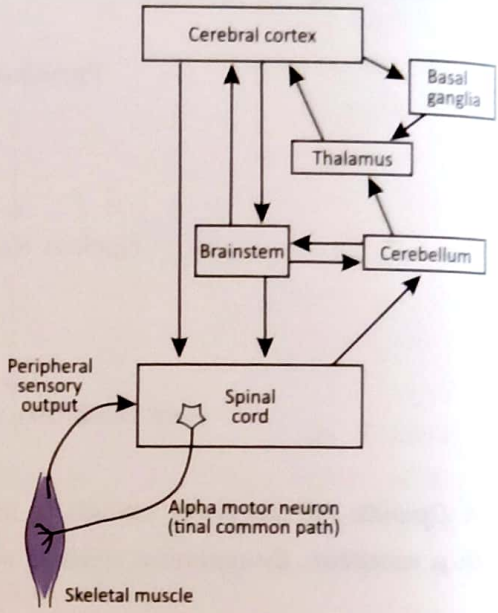
μ	κ	δ
Analgesia	Analgesia	Analgesia
Miosis	Miosis	
Sedation	Sedation	
Euphoria	Dysphoria	
Constipation	Diuresis	
Respiratory depression		
Growth hormone and prolactin secretion.		

Motor System

Motor cortex is in the frontal lobe.

MOTOR SYSTEM





→ Area 4 → primary motor cortex →
→ Area 6 → Premotor & supplementary motor cortex
→ Largest area of representation → Thumb, muscles of speech/vocalization and mastication.

Pyramidal Tracts → Include

→ Corticospinal : 30% fibers arise from Area 4, 30% from Area 6, 40% directly from parietal lobe. 3% of these fibers have Giant betz cells, rest are normal in size.

- Distal group of muscles
- Thumb muscles
- Control skilled voluntary movements and initiate voluntary movements

→ Corticobulbar
→ Cortico nuclear fibres

Extrapyramidal tracts

→ Vestibulospinal Tract → Controls posture and equilibrium
→ Reticulospinal tract → Controls trunk muscles
→ Rubrospinal tract → Controls intermediate muscles
→ Tectospinal → Controls movements in response to visual and auditory input.

Lateral corticospinal tract & Rubrospinal tract form lateral motor system.
Vestibulospinal, Reticulospinal & Tectospinal tract form medial motor system.

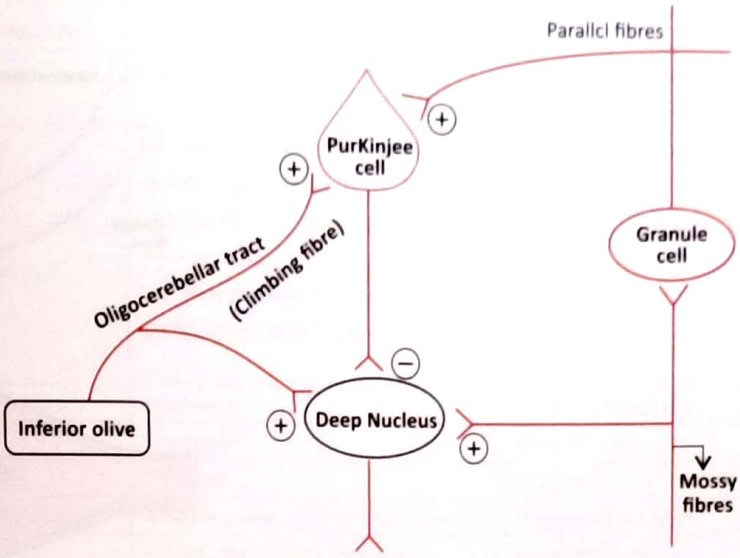
Cerebellum

1. **Vestibulocerebellum/ archicerebellum**
   → Controls posture and equilibrium
   → Eye Rotation with respect to head movement

2. **Spinocerebellum/ Paleocerebellum**
   → Co-ordination between muscle group, precise and smooth.

3. **Cerebellum/ Neocerebellum**
   → Sequence of muscle contraction.

Circuit of Cerebellum



→ 3 inhibitory interneuron which inhibit the purkinje cell
- Golgi cell
- Basket cell
- Stellate cell

→ Functional division of Nucleus
- Vestibulocerebellum → Nucleus Fastigius
- Spinocerebellum → Nucleus interpositus
- Cerebrocerebellum → Dentate nucleus

Basal Ganglia

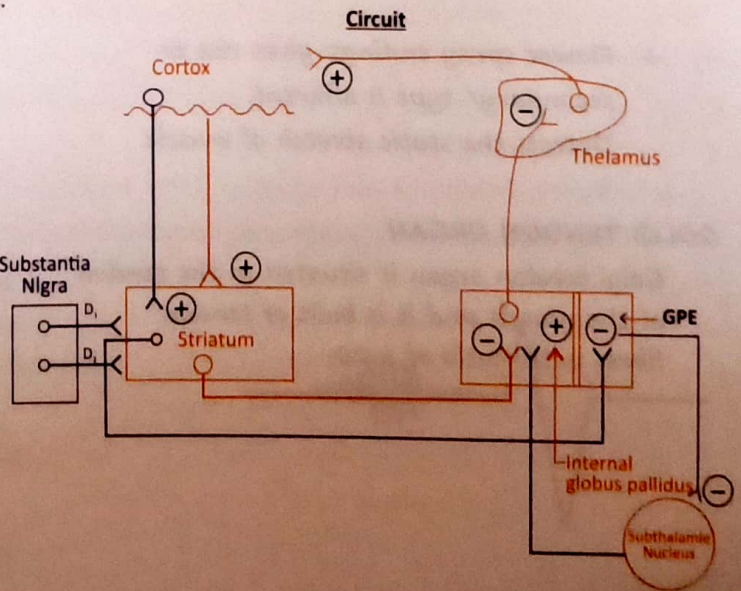
Parts

→ Caudate Nucleus } Corpus striatum
→ Putamen
→ Globus Pallidus
  - Internal globus pallidus
  - External globus pallidus
→ Substantia Nigra: Pars compacta & Pars reticularis.
→ Subthalamic Nucleus/ Body of Luys

DIRECT CIRCUIT & INDIRECT CIRCUIT:

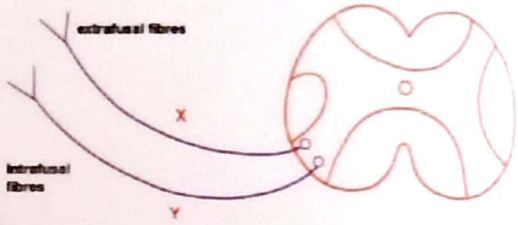
Direct Circuit -Pallidothalamic projection have background tonic inhibitory activity even at rest; In case of insult to basal ganglia such as in Parkinsonism is the basis of resting tremors.
  - facilitates movement.

Indirect Circuit: Inhibition of movement

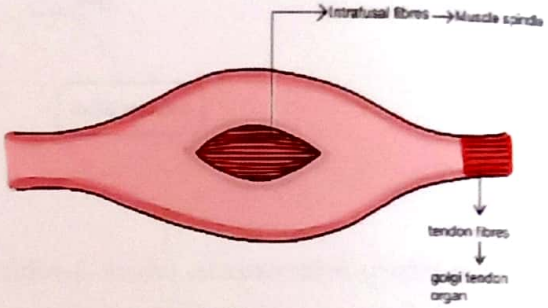


Substantia nigra is not involved in the direct or indirect circuit but modulates the activity of striatal neurons involved in the direct & indirect pathway via the nigrostriatal projections which are dopaminergic - D1 & D2. D1 - facilitate the direct circuit & D2 - inhibit the indirect circuit. Therefore in lesions of D1 & D2 projection, there is bradykinesia.

Lower Motor Neuron



Proprioceptor in the muscle



- → Muscle spindle detects the length of the muscle and rate of change of length of the muscle.
- → Rate of change of tension in the muscle is detected by Golgi tendon organ.

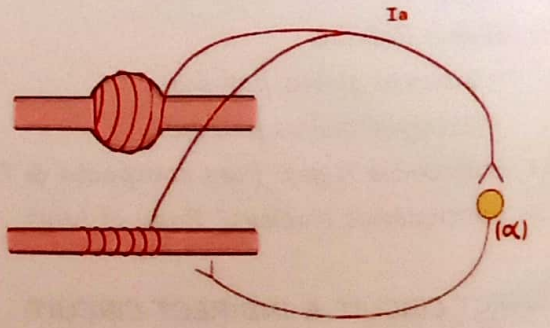
MUSCLE SPINDLE

Type of Intrafusal fibres

- → Nuclear bag
- → Nuclear Chain
- → 12 intrafusal fibre make 1 muscle spindle
  3 are nuclear Bag
  9 are nuclear chain

INNERVATION

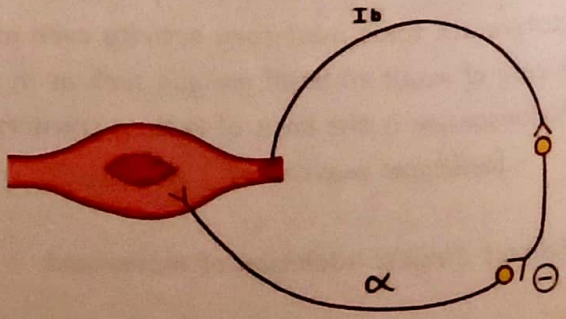
- → **Annulo-spiral endings** : joins to form primary/ Ia afferent.
  Circuit for dynamic stretch reflex (Knee jerk)
  Dynamic stretch reflex is a monosynaptic reflex.



- → **Flower spray endings**: gives rise to secondary/ type II afferent.
  Detects the static stretch of muscle.

GOLGI TENDON ORGAN

Golgi tendon organ is situated in the tendon of the muscle and it is built of tendon fibres with Ratio of 1:20



Nucleus Function Lesion

Nucleus	Function	Lesion
→ Supra optic → Paraventricular Nuclei	Synthesis of ADH Oxytocin	Diabetes Insipidus Delayed labor
→ suprachiasmatic nucleus	Circadian Rhythm	Jet lag syndrome
→ preoptic Nucleus	→ Anterior Neuron are androgen sensitive is (Regulated sexual function) → Posterior Neuron are estrogen sensitive	Loss of libido
→ Ventromedial Nucleus	Satiety	Hyperphasia
→ Lateral Nucleus	Hunger	Anorexia
→ Lateral Superior`	Thirst	Adipsia
→ Anterior hypothalamus	Warm sensitive Neuron	Hyperthermia
→ Posterior Hypothalamus	Cold sensitive Neuron	Hypothermia

SLEEP & EEG

5 type of waves

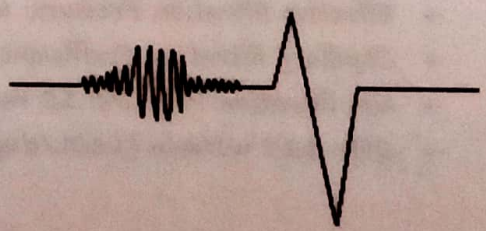
1. α Waves → 8 – 13 Hz → Quiet wakefulness
2. β Waves → 15-30 Hz → Alert wakefulness
   → REM sleep
3. Theta wave → 4-7 Hz → slow wave sleep
   → Recorded in tempo parietal region in children.
4. Delta wave → 0-4 Hz → Organic brain disease
   → Deep sleep
5. Gamma Oscillations → 30-70 Hz

REM sleep

→ Rapid eye movement
→ Irregular Heart rate and respiration
→ Penile erection
→ Loss of muscle tone
→ Dreaming, memory consolidation

Stage of Sleep

→ Slow wave Sleep → 15-20 Min (REM sleep)
→ Stage I → α wave
Stage II → Sleep spindle and large K complexes
→ Normal CSF pressure in lying down posture is
130 mm H_2O = 13 cm H_2O =10 mmHg
→ In sitting posture → 20 mmHg
60 drops/min or more on lumbar puncture
suggests increased CSF pressure.

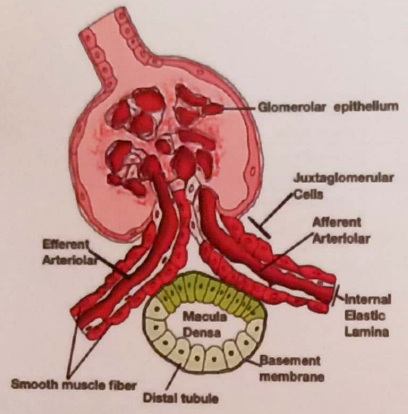


Kidney

There are two types of Nephrons:-

- → Cortical Nephrons (85%)- Forms Normotonic Urine.
- → Juxta medullary (Nephrons with long loops 15%) - Forms Hypertonic urine.

J-G apparatus



- → **Afferent arteriole (Granular cell or J G cell):-** Synthesis of Renin.
- → **Macula Densa cell** - (Cell lining early part of DCT): - Sensing of Na^+ and Cl^- in tubular fluids that reach the early DCT. It initiates-"Tubuloglomerular Feedback"! Adenosine is ligand for "Tubular Glomerular feedback"-
  Adenosine will go in afferent arteriole and will cause constriction of afferent arteriole, so less blood will come in Glomerulus and less filtration of Na^+
- → **Mesangial cell or Lacis cell or Goormaghtigh Cell:** - also involved in Tubulo-Glomerular feedback, alter vessel diameter and it is also Involved in Immune Complex formation.
- → **Type I Cortical Interstitial cell** - It synthesizes Erythropoietin

GFR (Glomerular filtration rate)

- → Glomerular Capillary Hydrostatic Pressure is 60 mmHg - It favors filtration (Elsewhere in the body it is 15 mmHg).
- → Plasma Colloid oncotic Pressure is32 mmHg + Bowman's capsule Hydrostatic Pressure is 18 mmHg they opposes the filtration at glomerulus so the Total
  Force that opposes the filtration is 50 mmHg
- → Effective filtration Pressure: 60-50 = +10 mmHg
- → Capillary filtration Coefficient = 12.5 ml/min/mmHg
- → Net filtration Pressure: 10 mmHg
- → GFR: 125 ml/min (180L/day)

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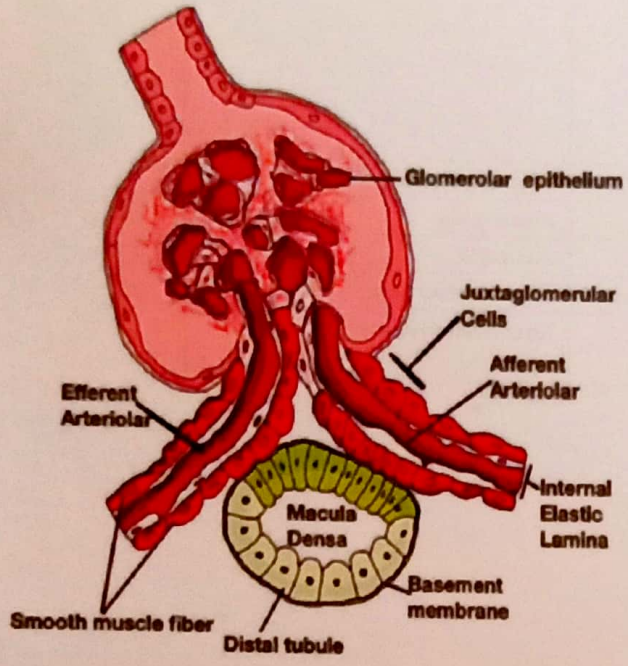

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Filtration Fraction:- (FF= GFR/RPF)

→ Renal Blood Flow (RBF) is 25% of cardiac output = 1250 ml/min

→ Renal Plasma flow (RPF) is 55%= 625 to 650 ml/min

→ Filtration Fraction = $\frac{GFR}{RPF} = \frac{125}{625}$ → 1/5th or 20%; Out of total plasma that flows in kidney; 1/5th filtration occurs into the glomerulus.

Factors influencing the GFR, RBF and filtration fraction

→ **Moderate Constriction of efferent arteriole**

- GFR ↑ (↑ Glomerular capillary hydrostatic pressure)
  RBF ↓ (Blood flowing out of glomerulus ↓ ;then blood coming in per unit time will also ↓ and therefore Filtration Fraction ↑ as it is → $\frac{GFR}{RPF}$

→**Sustained and severe constriction of efferent arteriole**

- GFR ↓ (because Proteins stay back in glomerulus capillaries)
- RBF ↓ so therefore Filtration Fraction remains same

→**Nephrolithiasis**

- ↓ Flow of tubular fluids therefore accumulate in capsule
- ↑ Bowman's capsule Hydrostatic Pressure and therefore GFR ↓
- Renal plasma Flow is Unchanged so Filtration Fraction ↓

Measurement of GFR

→ Best substance to measure GFR → INULIN, because it is freely filtered in glomerulus and neither reabsorbed nor secreted (excretion rate is same as filtration rate at glomerulus). There can be allergy to it, so commonly used substance to measure GFR → CREATININE, however creatine clearance is an over estimate of GFR by 5 – 10% because some creatinine also comes by Tubular secretion.

Creatine clearance is calculated by "Cockcroft and Gault formula":- $\frac{140 + x \text{ Age} \times \text{Bodyweight}}{72 \times \text{plasma creatinine}}$

→ Best substance to measure Renal blood flow or Renal plasma flow → PAH (Para-amino Hippuric acid) because once it comes in renal blood, then by filtration and secretion all of it comes into urine in single pass. Urine excretion rate of PAH gives Renal blood flow rate- because renal venous concentration of PAH is 0; which means all of it is cleared in urine in a single pass

Clearance = $\frac{ux \times v}{px}$

U_x → Urinary concentration of x in mg/ml

V → Volume of urine (ml/min)

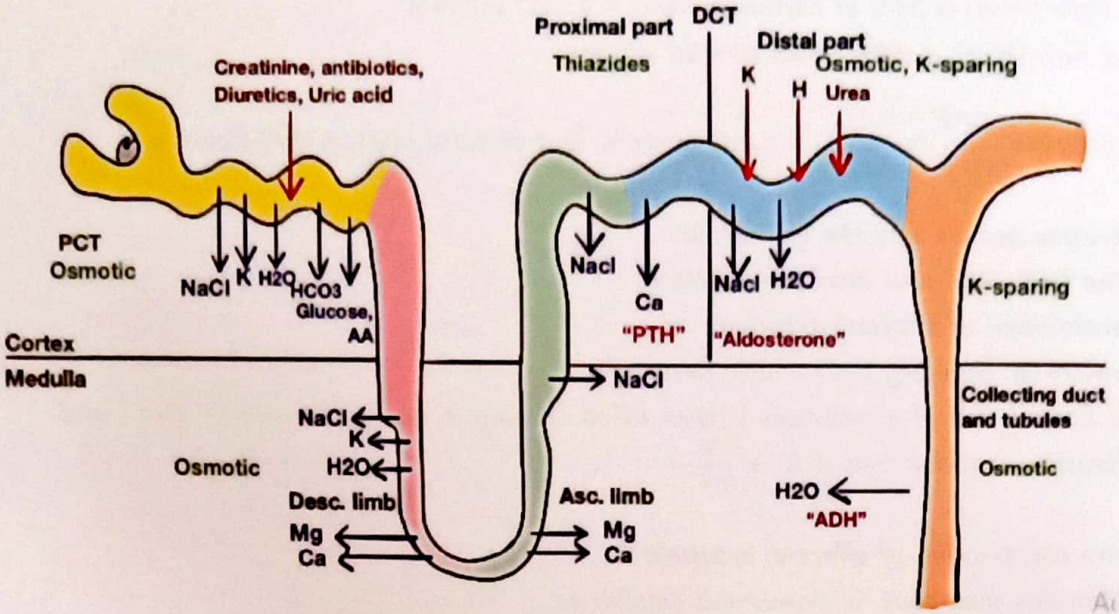
P_x → Plasma concentration of x mg%

$U_x \times V$ → It is total excretion of a substance into urine

Total Filtered amount = (P_x x GFR) Per unit time x

($P_x \times GFR$)< ($U_x \times V$) → Substance has be secreted

($P_x \times GFR$) > ($U_x \times V$) → It indicate reabsorption



PCT→ Glomerular filtrate is isotonic plasma and end of PCT it still remains isotonic, because(65% -70%) filtered Na^+ &65% -70% filtered water are reabsorbed from PCT. Equal proportion of Na^+ & H_2O are removed from glomerular filtrate.

- 100% Glucose is reabsorbed from PCT
- 100% Amino acids are reabsorbed from PCT
- 90% HCO_3^- is reabsorbed from PCT
- (70–75%) of K^+, Cl^- & Ca^{+2} are also reabsorbed from PCT.

Descending limb of loop of Henle

- There is movement of water by bulk flow so some Na^+ is removed

Thick ascending limb → it is impermeable to H_2O

- There is NKCC transporter: Na^+, K^+, CL^- are reabsorbed, but water is not reabsorbed therefore fluid that reaches early DCT will be hypotonic
- Thick ascending loop of Henle is called as diluting segment.

Collecting duct- it is concentrating segment of Nephron

- It concentrate the urine by action of ADH
- In Absence of ADH, 88% of filtered water is reabsorbed
- In presence of ADH, 99% of filtered water is reabsorbed.

Note:- Water reabsorption from PCT is called as Obligatory water reabsorption (65% - 70%)

- Water reabsorption from collecting duct is k/a facultative water reabsorption it depends on the osmolality of ECG whether ADH action will occur or not.
- In collecting Duct there are Principle - Inter cannulated cell (I-cell). Principle cell reabsorbs Na^+ & secrete K+
- Intercalated cell reabsorbs Na^+ & secrete H+ and whenever needed it can also secrete HCO_3^-. Therefore Intercalated cell is buffering cell in Kidney.
- Urinary acidification takes place in collecting duct.

Concentration of Urine

Mechanisms:-

→ Achieving hypertonicity in medullary interstitium

→ Role of ADH

Note:-

Hypertonicity in medullary interstitium is achieved& maintained by:

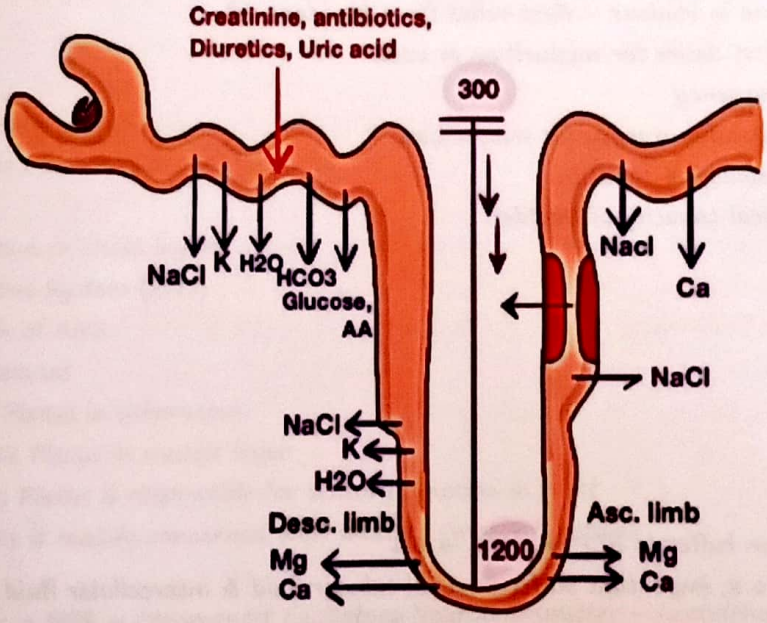
- Counter current multiplier
- Counter current exchange

Counter current multiplier mechanism

It will generate hypertonicity in medullary Interstitium

From thick Ascending limb of Henle medullary interstitium start becoming hypertonic, and gradually more and more solutes added& it starts becoming concentrated. The vertical osmotic gradient is 1:4

Renal physiology & diuretics



→ If Tonicity of medullary interstitium Ascending limb of Henle in 300 milli/Osmole/Litre then tonicity at tip of loop of Henle will be 1200 milliosmol/L (4 times) Max^m concentrating ability is 1200 mOsm/L

→ Horizontal osmotic Gradient across tubule in interstitium is 1:2, Tubular fluids are hypotonic (150 mOsm/L) and Interstitium (300 mOsm/L)

Counter current exchange is by vasa recta- It has sluggish flow so that solutes are maintained in the interstitium.

→ Vasa recta actually do not actively contribute in hypertonicity but they prevent the hypertonicity from dissipating.

One this has happened, AD it will finally remove water from collecting duct and make urine Concentrated

Urea contributes 40-50% to the total osmolarity in medullary interstitium.

Daily Urine Formation

→ Max^{m} concentrating ability ~ 1200 mOsm/L
→ Most dilute urine → 50 mOsm/L
→ Healthy adult excretes → 600 mOsm/day of solutes
→ Urine output needed → 0.5 Liters (Obligatory urine output)
→ Urine output < 400 ml ~ Oliguria
→ Urine output < 100 ml ~ Anuria

Note:-

→ If the urine is most dilute (50 mOsm/L) so to eliminate 600 mOsm/day over 24 hours, urine output needed → 12L/day
→ Max^{m} possible urine output → 18 L/day.

One liners of bladder

→ 50 ml of urine in bladder is called as residual volume
→ 100-150 ml of Urine in bladder – First reflex from bladder wall
→ 250 ml will cause first desire for micturition or void.
→ >400 ml will cause urgency
→ >600 ml will cause painful urgency for micturition
→ 800-900 ml is physiological capacity
1000 ml is anatomical capacity of Bladder.

Acid-Base Balance

3 Buffer systems

→ Chemical
→ Respiratory system
→ Kidneys

Chemical Buffers

- HCO_3^- - Most common buffer in ECF and pKa → 6.1
- Phosphate – pKa is 6.8, important buffer in renal tubular fluid & intercellular fluid.
- Proteins –pKa is 7.2

Note:-

→ 70% of intra cellular buffering is by Intracellular proteins.
→ Hemoglobin is extracellular Fluid Buffer.

Respiratory System

It is important in correction of metabolic alkalosis & acidosis.

Kidney: It buffers in 3 important ways

i) Reabsorption of filtered HCO_3^-
ii) Generation of New HCO_3^-
iii) Phosphate and ammonia buffers
→ Ammonia has pKa of 9.0 (highest pKa)

Reabsorption of Filtered HCO_3^- = $P_1 \times GFR$ = 24 mEq/L × 180 L/day

Total filtered HCO_3^- = 4320 mEq/day

→ Most of it is reabsorbed from PCT. Same amount of H^+ is secreted by PCT to reabsorb HCO_3^-

→ Total secretion of H^+ by Kidney is 4400 mEq/day out of which, 4320 mEq is for reabsorption of filtered Bicarbonate & 80 mEq that is excreted more in excess called as Net acid output.

Anion Gap

→ It is a Virtual Gap

$= (Na^+) - (Cl^- + HCO_3^-)$

$= 141 - (105 + 24)$

$= 141 - 129$

= 12 mEq/L (+/- 4 for K)

Therefore (8-16 mEq/L) is Normal Anion Gap.

Note:- In Acidosis HCO_3^- level ↓; Anion Gap ↑ but in such condition where anion of Acid is chloride, Anion Gap remains Normal.

G.I.T

4 layers

→ Mucosa

→ Submucosa

→ Muscularis Mucosa

→ Serosa

There are Plexus in these layers

Enteric Nervous System (ENS)

ENS is branch of ANS

There are two Plexuses

→ Meissner Plexus in submucosa

→ Auerbach's Plexus in muscle layer

→ Meissner's Plexus is responsible for sensory function in tract

→ Auerbach's is mainly concerned with motility (motor function)

Neurotransmitter in ENS → Commonest Excitatory Neurotransmitter – Acetylcholine & Substance P. Inhibitory transmitters in Enteric Nervous system → VIP, NO.

Pacemaker Cell in digestive Track – Interstitial cell of Cajal

This cell synapses to smooth muscle cell and synapses with ENS neuron.

Basal electrical Rhythm (BER)

→ The electrical activity is in the form of slow wave & there is a spike at the top of slow wave. This activity occurs at particular frequency called as Basal Electrical rhythm.

→ In stomach → 3-4/min

→ In Duodenum → 12/min

Jejunum → 9/min

Ileum → 7/min

→ The BER goes on decreasing from duodenum to ileum & this is known as the Law of the GUT, i.e. oral to anal direction of peristalsis.
→ In Colon, there is reversal of gradient i.e. BER frequency is higher in sigmoid and lower in ascending colon; this is Anti-Peristalsis which occurs from hepatic flexure of colon to caecum.
→ Ascending colon & half of transverse colon is called as absorptive colon. It absorbs all H_2O to form faecal matter, so there is peristalsis as well as anti-peristalsis. Remaining Part of colon is storage colon

Motor functions in digestive Tract

1. **Stomach**

→ Storage due to receptive relaxation of stomach wall.
→ 1-1.5 L without allowing intra gastric Pressure to rise much

2. **Mixing:** Occur because of retropulsion at Pylorus, Pyloric wall contracts so some amount of time it escapes & remaining goes back & escape. This is responsible for mixing & formation of chyme.

Normal Gastric emptying time is about 4-6 hrs and is longest for fat upto 8 hrs.

Factors

1. **Gastric Factor – Gastrin**: Promotes gastric emptying
2. **Duodenal Factors:** inhibits gastric emptying factors
   i) **Irritation of duodenal mucosa**
   ii) **Acidic chyme**
   pH has to be alkaline for Pancreatic Juices to act, Secretin is secreted in response to acidic chyme & it constricts pyloric sphincter.
   iii) **Hypertonic contents**
   Hypertonic contents entering duodenum further stops the gastric emptying.
   In absence of this, dumping Syndrome occurs.
   iv) **Fat in duodenum:** Fat prolongs gastric emptying by the release of CCK from duodenal cells.

→ ↓ Stomach contraction

Motility of Small Intestine:

1. **Fed State**

It is 2 types of Contraction
→ Segmentation - For mixing
→ Peristalsis - For Propulsion

2. **Fasting State**

→ Migrating motor complexes (House Keeper of Intestine)
→ Migrating Motor complexes clears the debris juices
→ 3 Phases of Migratory motor complex
→ Entire Cycle - 90 min
→ Hormones that strengthens the MMC contraction: **Motilin**
- Drug that binds to Motilin receptors is: Erythromycin & given as Pro-Kinetic agents.

REGULATORY SECRETIONS OF DIGESTIVE TRACT

Stomach

Cell	Secretion	Function
1. ECL Cell (Enterochromaffin)	Histamine	Act via H_2 Receptor → ↑ Gastric acid secretion → Potentiating effect on 2 stimuli - Gastric - Acetylcholine
2. G-Cell in Pylorus	Gastrin	↑ Gastric acid secretin & ↑ Gastric motility
3. D cell in pylorus Delta cell pancreas Hypothalamic neurons	Somatostatin	→ ↓ Gastric acid secretion → ↓ Insulin & Glucagon secretion → Growth hormone Inhibiting hormone
4. I Cell	CCK	→ Enzyme rich Pancreatic Juice secretion → ↓ Gastric Motility → ↑ Intestinal Motility → Cholagogues → ↑ flow of bile
→ S. cell (duodenum)	→ Secretin	→ Maintains alkaline PH. → Secrete HCO_3^- rich Pancreatic juice → ↓ Gastric emptying (does not allow acidic chyme to come in duodenum.)
→ GI mucosa	→ Incretins - GIP (Gastric Inhibitory Peptide) / Gluco-insulinotropic peptide - GLP	→ Incremental Insulin secretion
→ Vagal stimulus on G Cells	→ Bombesin (gastrin releasing peptide)	→ Neurotransmitter (instead of acetylcholine)
→	→ GIP (Gastric Inhibitory Peptide) / Gluco-insulinotropic peptide	→

→ Cholagogues ↑ flow of bile and cause Gall Bladder Contraction
Choleretics → ↑ Bile secretion from liver (Bile acids, Vagus Nerve)

DIGESTIVE SECRETIONS:

1. SALIVA:

Primary salivary secretion: Isotonic rich in Na^+, Cl^- & Water;

Final salivary secretion: when primary secretion flows through the duct, there is ductular modification, i.e. Na^+ is reabsorbed & K^+ is secreted;

Cl^- is reabsorbed & HCO_3 is secreted.

It duct is impermeable to water.

Rich in K^+, HCO_3 , H_2O & is Hypotonic.

→ If ↑ flow rate of Saliva, then there is no time for ductular modification & in that case salivary composition resembles primary secretions.

Composition of Saliva:

→ Hypotonic to plasma

→ pH: 6-6.5

→ Contain: K^+, HCO_3^-

→ Enzymes: Ptyalin (Salivary Amylase)

→ Lingual lipases

2. GASTRIC JUICE

→ Pyloric Glands have "G" Cells which secrete gastrin.

→ Mucous Neck Cells → Mucin

→ Peptic/ Chief cell secrete Pepsinogen which converts into Pepsin

→ Parietal Cell → Secrete HCl &Intrinsic Factor

→ Pepsin: 10-20% protein digestion starts in the stomach by action of Pepsin ;Digests the meat collagen

→ Gastric Lipase: Very weak lipase

→ Renin: Milk Protein.

Phases of Gastric acid Secretion

1. **Cephalic Phase:** 20% secretion of Gastric acid occurs in cephalic phase
   It is mediated by vagus
2. **Gastric Phase of Gastric acid secretion**

→ 70% of total secretions occurs in Gastric phase

→ It is mediated mechanically & chemically

→ Mechanically by distension of stomach wall

→ Chemically, by the protein break down products

3. **Intestinal Phase:** 10% Gastric acid secretions occurs in intestinal phase.

3. PANCREATIC JUICE

Two types

i) HCO_3^- rich: secreted under the influence of secretin

ii) Enzyme rich: secreted under the influence of CCK.

1st enzyme to be activated in Pancreatic Juice is **Trypsin**

→ Trypsinogen in duodenum $\xrightarrow{\text{enterokinase}}$ trypsin
→ Chymotrypsinogen $\xrightarrow{\text{Trypsin}}$ Chymotrypsin
→ Trypsin and Chymotrypsin are **endopeptidases** - break some internal bonds of protein
→ Carboxypeptidase & Amino peptidases are **Exopeptidase** - break exterior bonds of Protein
→ digests all the nutrients
→ It has highest pH of 8-9
→ **Note:** Lowest pH is **Gastric Acid**
→ Pancreatic Juice has all the enzymes e.g. Amylase, trypsin, Chymotrypsin, carboxypeptidase, lipase, co-lipase, Phospholipase, Nuclease, Ribonuclease.
→ Amylase is 40 times more potent than salivary Amylase.
→ Co-lipase prevents the inactivation of lipase by the bile salts.
→ Pancreatic secretion also show 3 phases:
I. Cephalic
ii. Gastric
iii. Intestinal : > 70% secretions of pancreatic juice comes in intestinal phase.

4. Gall Bladder & Bile

Gall-bladder

i. It stores Bile
ii. Concentration of Bile
iii. Acidifies Bile
iv. Add mucous to Bile

IMPORTANT ASPECTS OF ABSORPTION AND DIGESTION

→ **Carbohydrate Digestion**:
- Polysaccharides $\xrightarrow{\text{saliva}}$ oligosaccharide $\xrightarrow{\text{Pancreatic juice}}$ disaccharides $\xrightarrow{\text{disaccharidases (sucrase, maltase, lactase)}}$ mono saccharides (absorbed from intestine).

→ **Protein Digestion:** Polypeptides $\xrightarrow{\text{pepsin}}$ Oligopeptides $\xrightarrow{\text{pancreatic proteases}}$ Di & Tripeptides $\xrightarrow{\text{Succus Entericus}}$ amino acids

3. Fat Digestion: Short chain fatty acids are absorbed directly into **portal Blood**
→ But long chain fatty acid are acted upon by action of Bile
2 Action will be performed by Bile on Fats
i. Emulsification (↑ surface area of fat)
ii. Micelle formation (Micelle will carry fat digestion products and help in absorption)
→ All nutrients are absorbed in **Portal Blood** except long chain fatty which are not water soluble are absorbed in the lymphatics of intestine (lacteals) in form of Chylomicrons, and from lymphatics into blood

Stomach

→ Alcohol is absorbed from stomach

Duodenum

→ All Divalent cations are absorbed from duodenum except magnesium e.g. Iron, calcium.

Jejunum

→ All the major nutrients are absorbed from jejunum.
→ 6.6 L/day water is absorbed from jejunum and only 1.5 L/day absorbed from colon.

Ileum

→ Mg^{++}, Vit B12, Bile salts & Antibodies in Newborn are absorbed from ileum.
Colonic Microflora synthesize Vit K, B12, folic acid and short chain fatty acids.

Endocrine

Hormones:

	Peptide hormones	Steroid hormones	Derivatives of Tyrosine
Hormones	G.H Insulin Glucagon	Corticosteroids Aldosterone, Estrogen Progesterone Testosterone	Thyroid Catecholamines
	Not lipid soluble	Lipid soluble	
Receptors	present in cell membrane	Intracellular – either in cytoplasm or in Nucleus.	Catecholamine -cell membrane receptors (GPCR) Thyroid hormones – intra Nuclear receptors

Peptide hormones

→ Short ½ life.
→ Exception – Insulin like growth factor has long ½ life as it is bound to Plasma Proteins (IGF Bps)
→ synthesized and stored inside the cell
→ stimulus is for their secretions.

Steroid

→ Long ½ life.
→ Not stored, they are immediately released into circulation
→ stimulus is not for their secretion but for their synthesis.

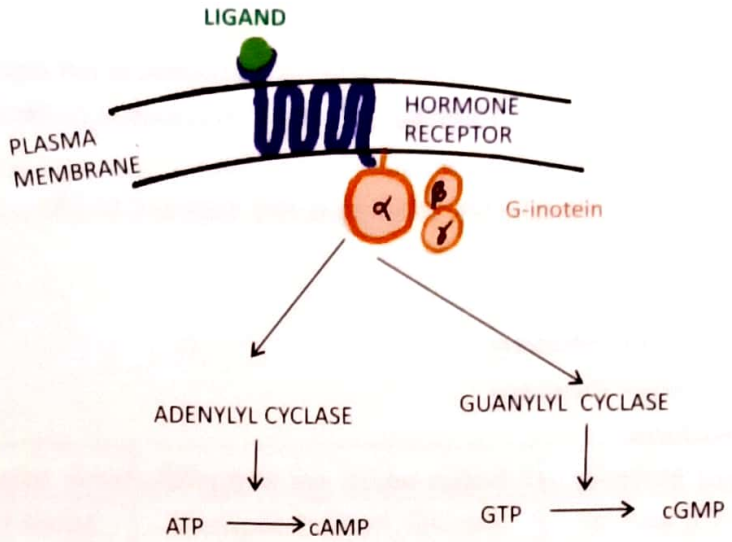
Receptors for Peptide Hormones

Cell membrane receptors are of 2 types

1. G – Protein coupled Receptors
2. Catalytic Receptors

G-protein coupled Receptors

Receptor is coupled with G: Protein (7 trans member segments)



When Peptide molecule comes it binds to receptor; Then G Protein (sub units α, β, γ) α sub unit will dissociate and activate enzyme (adenylyl cyclase or guanylyl cyclase enzyme)

ATP → cAMP

GTP → cGMP

These acts as secondary messengers in the cell they will activated protein Kinases and those protein Kinases act on certain amino acid residues & that will exert effect of those Hormones.

cAMP is secondary messenger for	cGMP is secondary messenger for
ACTH	ANP
TSH	Nitric oxide
FSH	
LH	
PTH	
Glucagon	

Catalytic Receptors

1. Tyrosine Kinase receptor eg Insulin receptor
2. Tyrosine Kinase associated receptor e.g. Growth Hormones

The only difference b/w these is GH receptors itself not have activity but it's cytoplasmic tail is linked to tyrosine kinase receptor.

In addition to this, it also activates JAK/STAT machinery that will exert effects of growth Hormone.

Steroid receptors

- → steroids receptors are intra-cellular
- → many of them have intracytoplasmic receptor
- → Steroid hormones combine with these receptors and this complex enters Nucleus and bind with specific sites on the DNA stands called as Hormone response elements (HREs) in nucleus.

Imp points

- → Shortest ½ life is of catecholamine's
- → Longest ½ life is for steroid Hormones Vitamin D (15 days) > Thyroid Hormones (7-8 days)
- → Shortest latency for onset of action is for Oxytocin (few seconds)
- → Longest latency is for thyroxine (48-72 hrs)
- → Shortest peptide Hormone – TRH

→ Longest Hormone – HCG, GH

→ Only Hormone Stored in extra-cellular site – Thyroid Hormone in follicles.

→ Thyroid Gland is not essential to life. Parathyroid Gland is essential to life if serum Ca^{+} falls below 6 there will be Laryngospasm.

Adrenal cortex is essential to life adrenal medulla is not essential to life.

Pituitary Gland

1. Adenohypophysis - Anterior Pituitary
2. Neurohypophysis - Posterior Pituitary
   - Secretes ADH, Q oxytocin
   - Both are synthesized in Nerve cell bodies which are in hypothalamic Neuron and then come down to Neurophysin
   - ADH & Oxytocin are carried to terminal endings in posterior Pituitary and released in circulation

These terminals endings are called as "**Herring bodies**"

ADH (**Vasopressins**) actions -

i. Vasoconstriction

ii. Water reabsorption

ADH has 2 type of receptors V_1 & V_2

Action on V_2 receptors in collecting duct cause insertion of aquaporins channels and cause water reabsorption

Oxytocin functions

i. Parturition

ii. Milk ejection reflex

It is also involved in degradation of corpus ileum.

→ **Intermediate lobe of Pituitary** secretes POMC (Pro-opiomelanocortin)

It is cleaved to form corticotrophin, ACTH and β-LPH

ACTH is further cleaved into MSH, CLIP

β-LPH further cleaved into endorphins.

→ ACTH and MSH share 1st 13 amino acids on one end and therefore ACTH has MSH like activity

Therefore in Addison's disease, Pigmentation occurs due to increased ACTH

Anterior Lobe (Adenohypophysis)

2 types of cells

1. Chromophobe Cells (50%)
2. Chromophil cells are of 2 types: **Acidophil cells (70-80%) & Basophil cells (20-30%)**

- Acidophil cell secrete GH & Prolactin
- Basophil cell secretes, FSH, LH, ACTH, TSH

Hormones Secreting cells of anterior pituitary

- Somatotropes (40-50%) - secrete GH
- Corticotropes (20%)
- Lactotropes (5-10%)
- Gonadotropes (5-10%)
- Thyrotropes (5-10%)

→ All the hormones are excitatory as well as inhibitory control except Prolactin which is under Inhibitory control from Hypothalamus.
there is Prolactin Inhibiting factor from hypothalamus.

- Thyrotropin releasing Hormone is said to be Prolactin releasing factor.

Growth Hormone: Growth Hormones is Diabetogenic Hormones

Diabetogenic Hormones

→ GH
→ Glucagon
→ Cortisol

GH	Glucagon	Cortisol
Growth Hormones ↑ Blood Glucose by Preventing Peripheral Utilization of Glucose	Glucagon ↑ Blood Glucose by glycogenolysis	It ↑ by gluconeogenesis (Producing Glucose from Non carbohydrate sources)

3 types of Diabetes

1. **Pituitary Diabetes**: caused by growth Hormone, it is only weekly sensitive to insulin.
2. **Adrenal Diabetes**: Due to excess of Glucocorticoids is moderately sensitive to insulin.
3. **Pancreatic Diabetes**: It is strongly sensitive to insulin.

Growth Hormone Disorders

1. Excess GH
   - before puberty – Gigantism
   - after puberty - Acromegaly
2. Deficiency of GH
   → before puberty - Dwarfism
   → after Puberty – Acromicria
   → Dwarfism with deficiency of GH is Pituitary Dwarfism
   → Dwarfism with Normal GH is Levi-Lorain Dwarfism seen in Africans pigmies
   GH normal but there is deficiency of somatomedin C / Ig1
   → Dwarfism with ↑ GH → Laron Dwarfism
   - There is receptor insensitivity

Thyroid Hormones

Synthesis

- Iodides in diet are trapped by thyroid gland
- transporters NIS($2Na^+$: 1 Iodide) and Pendrin transports iodine into the follicle
- Tyrosine + Iodine → monoiodotyrosine (+ iodine) → Diiodotyrosine
- coupling & condensation reaction to form T3 & T4
  Important enzyme involved is peroxidase enzyme
- 90% secretion of Gland is T4 and T3 in 10%
- In periphery, T4 → T3 which exerts action of thyroid hormone
- T4 hormone provide large and stable pool of thyroid hormones in body as daily Turnover rate of T4 is 10%

Note: Daily turn over rate of T3 – 70%

Half life of T4 = 7-8 days

→ More extensive plasma binding is shown by T4

Calcium Homeostasis

Calcium Homeostasis is under 3 Hormones:

1. Parathyroid Hormone
2. Calcitonin
3. Vitamin D

There are 3 organ system involved in calcium Homeostasis:

→ Bone

→ Kidney

→ GIT

PTH

↓ Serum Ca^{++} → stimulate PTH.

Receptors are located on osteoblasts which get differentiated into osteoclasts and remove Ca from bone

Functions -

→ removal of Ca^{++} from Bone by bone resorption

→ PTH Hormones ↑ Ca^{+2} reabsorption from renal tubules & cause phosphaturia

Ca phosphate Product is Constant about 40-50

→ PTH Potentiates action of Vitamin D which cause Ca^{++} absorption from gut.

It is referred feed forward action.

Ca^{++} in body is of 3 types

1. 45% is free or diffusible Ca^{++}
2. 45% is Combined with albumin in Plasma
3. 10% is combined with other complex like citrate, Phosphate

Tetany Manifestations: Resulting from Hypocalcemia are:

→ **Trousseau's Sign** - When B.P cuff is applied to arm there will be carpopedal spasm

→ **Chvostek's Sign** - tap over angle of mandible and facial muscle goes in spasm

Note:- First Manifestations of tetany will appear when serum Ca^{++} falls below 7.

→ Death will occur when Ca^{++} falls below 6 due to laryngospasm